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ORIGINAL ARTICLES

RICKETS, DEFICIENCY OF "ALKALINE" PHOSPHATASE ACTIVITY AND PREMATURE LOSS OF TEETH IN CHILDHOOD

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ALTHOUGH there is a wide range of individual differences in enzyme activity in the blood[1-5] and tissues of children, an almost total deficiency in the activity of a particular enzyme can rarely be demonstrated. Metabolic disorders, such as phenylpyruvicaciduria, alkaptonuria and albinism, are thought to be an expression of a deficiency of an enzyme or enzymes involved in the metabolic cycle of certain compounds, although the exact natures of these disorders are not yet clear.[6] Abnormally low alkaline phosphatase activity is usually associated with scurvy[7] and with hypothyroidism,[8] but has been reported in three children, in all of whom skeletal disease was an essential feature. Rathbun's patient[9] died at three weeks of age, showing marked rarefaction of the skeleton and an obscure disease of the kidney. Schneider and Corcoran's patients,[10] brothers aged 10 and 13 years, had bowed legs and evidence of possible renal impairment. Hansen[11] reported a case diagnosed as osteogenesis imperfecta associated with low alkaline phosphatase activity in the bone.

The present report deals with studies carried out during more than two years with a child having almost complete lack of alkaline phosphatase activity, a skeletal disease resembling rickets, and premature loss of teeth.

MATERIALS AND METHODS

Alkaline phosphatase activity was determined under rigorously controlled conditions by the micromethod of Bessey, Lowry and Brock,[12] which utilizes *p*-nitrophenylphosphate (NPP) as substrate. The incubation mixture was adjusted to pH of 10.4 for measurement of activity of plasma and of ground, autolysed tissues. Taurocholate inhibition studies were conducted under conditions

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previously reported.[4] Definition of Bessey-Lowry plasma unit has been adapted to apply to tissues by expressing results on the basis of kg. of wet tissue. Serum inorganic phosphate was measured by a microcolorimetric modification of Fiske and Subbarow procedure.[13] Calcium content was assayed by digestion of plasma with nitric acid followed by analysis in a Weichselbaum-Varney flame-photometer or by precipitation and titration. Most of the blood samples were collected by finger puncture. Plasma and tissues were preserved at —30°C. and when transported in dry ice were cleared of CO_2 before analysis.[14]

The Patient

Patient was first seen when she was 19 mo. of age. Six weeks previously several teeth had become loose, and in the interval 6 teeth had been shed spontaneously. When the teeth began to fall out for the first time legs seemed to be painful and increasing deformities had developed.

Mother had been troubled by vomiting during last 6 mo. of pregnancy, but had gained weight normally and was in good condition at end of gestation. Infant was delivered uneventfully at term, weighing 3.0 kg. Infant gained weight well and had been in good general health despite frequent vomiting during 1st 6 mo. of life. History gave no evidence of outstanding dietary deficiencies. Intake

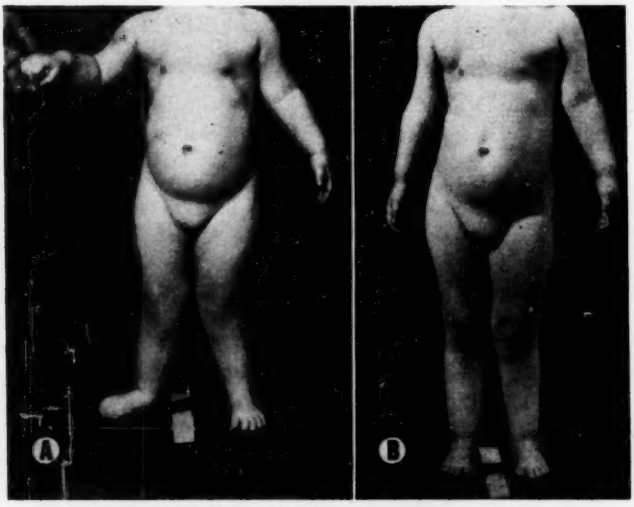

Fig. 1. A. Patient at 22 mo. of age. B. At 39 mo. of age.

of vitamin D had been 1600 u. daily in 1st 18 mo. and then 4000 u. daily. Supplement of ascorbic acid had been increased from 80 to 180 mg./day when teeth first became loose. Family history revealed that a paternal great-uncle was short in stature and had some skeletal deformity; one of his 2 sons was similarly deformed.

Physical examination showed a well-nourished infant whose height and weight were within normal limits (Fig. 1). She had marked knock-knees, bowing of femurs and tibias, enlarged wrists, Harrison's groove and a protuberant abdomen. Head was of normal appearance. Eyes and optic fundi were normal. Six deciduous teeth were present; these were very small and 2 of them were loose. Upper and lower central incisors and upper lateral incisors were absent. Gums were normal. Heart, lungs and blood pressure were normal. Liver and spleen were palpable; this was thought to reflect the deformity of the chest. Muscle tone was only fair. There were no neurologic abnormalities.

RGs showed poor mineralization of long bones, ribs, jaws and teeth. There were focal symmetric defects in metaphyses of major long bones (Fig. 2). These were most pronounced at the sites of most rapid growth: at distal ends of radius and ulna, proximal end of humerus, distal end of femur and proximal ends of fibula and tibia. Spongiosa appeared to be reduced and architecture of cortex

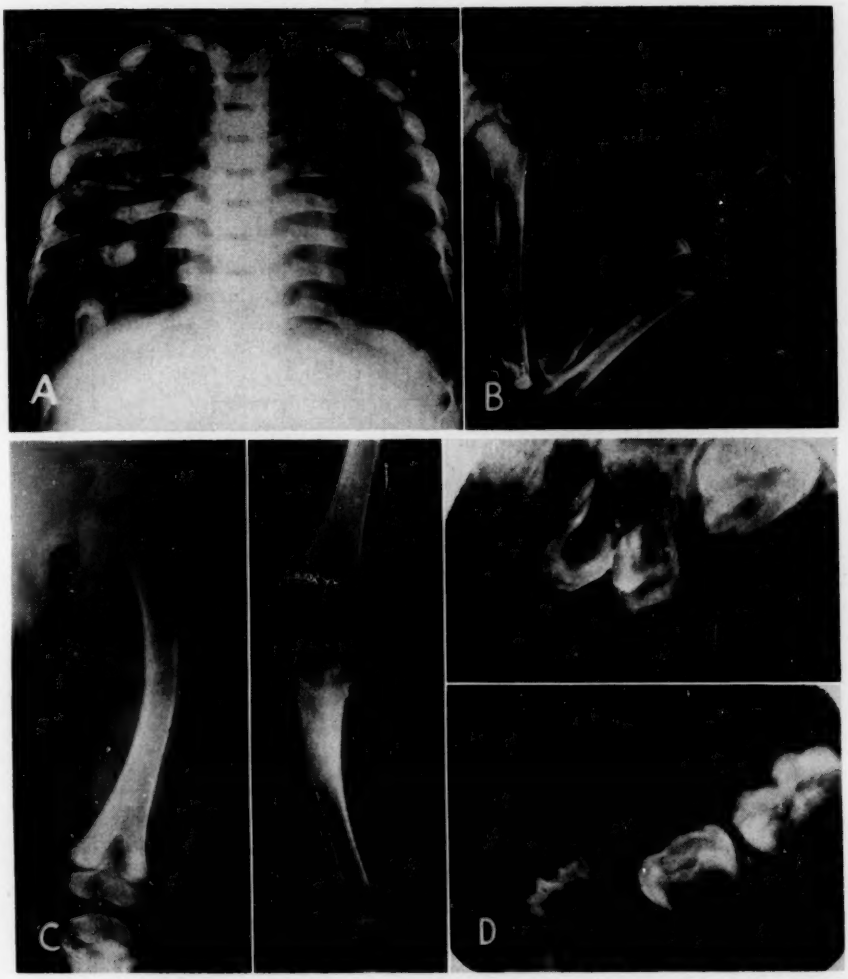

FIG. 2. RGs of patient. A. Chest, showing poor mineralization and flaring of sternal ends of ribs. B. Arm, demonstrating metaphyseal defects and poor mineralization. C. Leg, showing bowing and cortical new bone formation. Irregular calcification at metaphyses is most evident at proximal end of tibia and fibula. D. Teeth; irregular calcification and large pulp cavities are evident.

was coarse. There was a distinct brush border at distal ends of radius, tibia and fibula. Femurs were bowed laterally and tibias were bowed medially; concavities were filled in with cortical new bone formation. Sternal ends of ribs were flared and irregularly mineralized. There was irregular calcification of deciduous and permanent teeth. Calvaria and vertebrae appeared to be normal.

There was no laboratory or clinical evidence of liver or of intestinal disease. Kahn tests of patient and her parents were negative. Tuberculin test was negative. Urine was normal and did not contain an excess of Ca (5.5 mg. in 20 hr. on a low calcium intake). An excretion of more than 50 mg. in 24 hr. would have been considered excessive. Renal function was adequate as judged by normal serum NPN (30 to 36 mg./100 cc.), urea clearance, excretory urogram and ability to concentrate

urine (specific gravity 1.014 to 1.027). Serum pH, Cl and CO_2 content were normal. Serum ascorbic acid level was 1.24 mg./100 cc. Oral glucose tolerance test was normal. Serum protein was 6.3 gm./100 cc. (albumin 4.3, globulin 2.0).

Serum Ca was normal (9.8 to 10.3 mg./100 cc.). Serum inorganic phosphate was within normal limits (5.3 to 6.0 mg./100 cc.). Red cell organic-acid soluble phosphate was at upper normal levels, total being 61 mg. and adenosine triphosphate 13 mg./100 cc. packed red cells.* Serum alkaline phosphatase activity was consistently low, 0.8 to 1.64 NPP (Bessey-Lowry) u., or 1.44 to 2.95, expressed as Bodansky u.

Alkaline Phosphatase Activity of the Plasma and Tissues

Figure 3 shows the alkaline phosphatase activity of the patient's plasma in relation to that of normal girls of the same age. It will be noted that the values found for the patient were far below even the lower limit of normal, which at 2 years is 3.88 NPP u., with a mean value of 6.6 u.[4] The alkaline phosphatase activity of the plasma of normal children

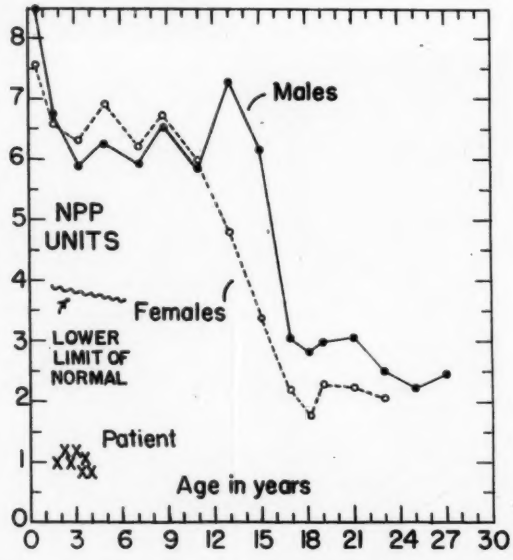

Fig. 3. Mean values for plasma alkaline phosphatase activity, NPP u., for boys and girls, plotted against age in years. Lower limit of normal for girls is shown. Measurements of patient's plasma are shown by crosses.

is inhibited about 50% in the presence of taurocholate.[4] The alkaline phosphatase activity of extracts of bone and kidney is reduced approximately 50% by taurocholate, while that from intestine retains 80 to 100% of its activity.[4, 15, 16] The enzyme activity of the patient's plasma was reduced to 68% in the presence of taurocholate, indicating that at least some of the plasma enzyme was derived from sources other than bone. An exfoliated tooth was found to contain no alkaline phosphatase activity.

Biopsy specimens of liver and a rib were obtained from the patient.† Their alkaline

* Determinations were made in the laboratory of Dr. George M. Guest.

† Biopsies were performed by Dr. C. Marshall Lee, Jr.

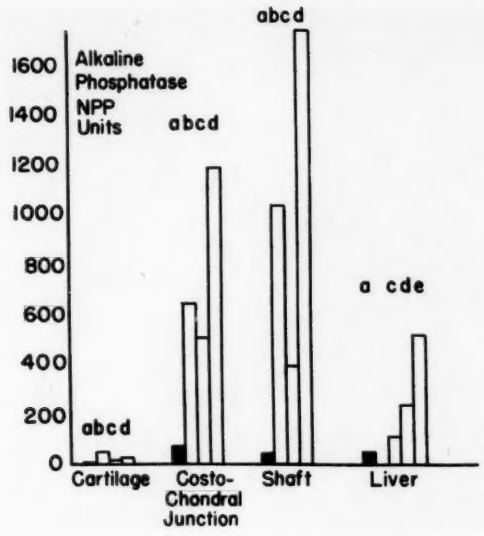

FIG. 4. Alkaline phosphatase activity, NPP u./kg. wet tissue. Values found for patient are indicated by black columns (a). Columns b, c and e represent findings in tissues of children who were free of skeletal disease; column d represents child who had active rickets.

phosphatase activity was compared with that of similar tissue obtained from four other children at surgery or autopsy. Figure 4 shows the results, indicating that all the values for the patient's tissues were low in relation to those found for the other children. Determinations were made on samples of rib taken from the cartilage, from the bone and directly at the costochondral junction. The bone was carefully freed of marrow. At the costochondral junction the value for the patient was 79 NPP u./kg. tissue, as compared to 510 and 645 NPP u. found in two children without skeletal disease, and 1190 in a child with active rickets. The findings for the liver were similar: 49 NPP u. for the patient, 109 and 500 for two children without skeletal disease and 233 u. for the child with rickets.

HISTOLOGY OF THE RIB

Figure 5 shows the histologic appearance of the costochondral junction obtained at biopsy. The section was prepared without decalcification and stained with hematoxylin eosin. The lesion appeared exactly like that of vitamin D-deficient rickets. The changes characteristic of rickets were present in the cartilage. The osteoid borders of the trabeculae were markedly developed. There were abundant osteoblasts which appeared to be morphologically normal.[17] *

POSSIBLE ETIOLOGY OF THE DISORDER

Search for a Toxic Substance: Since alkaline phosphatase activity is inhibited *in vitro* by a variety of substances,[18] a search was made for a toxic material which might have impaired the enzyme. A particular search was made for evidence of exposure to beryllium, which is a powerful inhibitor of alkaline phosphatase activity *in vitro*[19, 21] and which also

* Section was prepared and examined by Drs. Edwards A. Park and Richard Follis.

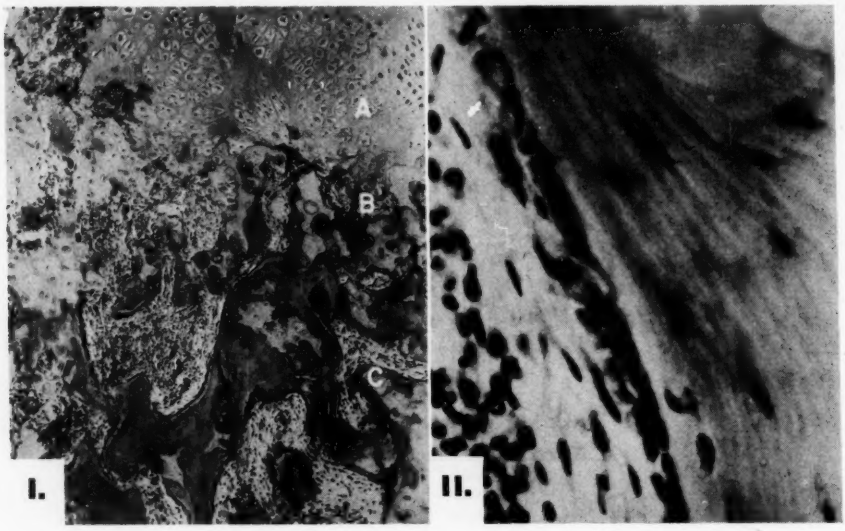

FIG. 5. Photomicrographs of sections prepared from undecalcified costochondral junction and stained with hematoxylin-eosin. I. × 100. Note disorganized cartilage (A), absence of distinct line representing cartilage-shaft junction (B) and abundant osteoid (C), which is covered by osteoblasts. II. × 450. Osteoid is bordered by osteoblasts of normal appearance.

inhibits the calcification of rachitic cartilage *in vitro*.[22,23] There was no history of pica. Metal turnings with which the father worked on occasion were found to contain 0.0034% of beryllium.* Spectographic analysis† of the child's urine failed to show an abnormal concentration of lead, arsenic, mercury, fluorine, manganese, tin, copper, silver, cadmium, zinc or beryllium. A tooth contained no excess of fluorine.† The alkaline phosphatase activity of the patient's plasma, like that of a normal child, was essentially unaltered by dialysis against NaCl 0.9%. When the patient's plasma was mixed with that of a normal person, the alkaline phosphatase activity was the average of the two values measured separately. Thus there was no inhibiting substance in the child's plasma interfering with the measurement of alkaline phosphatase.

Search for Increased Excretion of Phosphatase: The absence of excessive amounts of alkaline phosphatase activity in the urine (0.08 NPP u.) or in the saliva (0.17 NPP u.) indicated that it was not being lost by these routes.

Search for a Genetic Factor: The alkaline phosphatase activity of the plasma of the mother, two maternal aunts and the maternal grandmother was normal (table 1). The father's plasma alkaline phosphatase activity was abnormally low, 1.1 NPP u. (mean for men of his age, 2.16, standard deviation 0.41[24]). None of the paternal relatives consented to examination.

THERAPEUTIC EFFORTS

Several attempts were made to increase the alkaline phosphatase activity, in the hope

* Analyses were performed in the Kettering Laboratory of Applied Physiology of the University of Cincinnati.

TABLE 1

Plasma Alkaline Phosphatase Activity

Subject	Age	NPP/u.	Bodansky/u.	Skeleton Affected	Teeth Affected
Patient 1	18–30 mo.	*0.8–1.6*		Yes	Yes
Mother	27 yr.	2.38		No	No
Mother's sister	25 yr.	2.07		No	No
Mother's brother	30 yr.	1.74		No	No
Mother's mother	52 yr.	2.34		No	No
Father	35 yr.	*1.01*		No	No
Father's uncle	65 yr.	—		Yes (dyschondroplasia)	?
Father's uncle's son	30 yr.	—		Yes (dyschondroplasia?)	No
Patient 2	20 mo.	*0.52*		Yes	Yes
Brother	3 yr.	(*1.8*)	3.3	No	No
Mother	23 yr.	(*0.33*)	0.6	No	No
Father	24 yr.	—		No	No
Patient 3*	6 mo. (d. 8 mo.)	(*0.16, 0.9*)	0.3, 1.6	Yes	—
Patient 4†	2½ mo. (d. 8 mo.)	(*0.5, 1.55*)	0.91, 2.8	Yes	—
Sister	9 yr.	4.56		No	No
Mother		*0.59, 0.42*		No	No
Father		*0.95, 1.11*		No	No
Patient 5‡	6½ mo.	*0.69*		Yes	Yes
Mother		*0.77*		No	No
Father		*0.51*		No	No
Maternal aunt		—		"Disease of hip"	No
Patient 6§	8½ yr.	*0.83*		Yes	Yes
Sister	2½ yr.	—		Yes	Yes
Sister	4½ yr.	3.04		No	No
Sister	6$\frac{7}{12}$ yr.	—		Yes	Yes
Mother		—		No	No
Father		—		No	No

Summary of plasma alkaline phosphatase activity and of presence or absence of skeletal and dental disease in families of several patients. Values for alkaline phosphatase are given in units of method which was used in making determination. Measurements which were made in Bodansky u. have been translated into NPP u. (1 NPP u. is equivalent to 1.8 Bodansky u.); these are enclosed in parentheses. Abnormally low values are italicized.

* Patient of Drs. Butler and Gertrud C. Reyersbach.

† Patient of Dr. Warren E. Wheeler.

‡ Patient of Dr. Luigi Luzzatti.

§ Patients of Dr. Samuel W. Clausen.**

** Deceased.

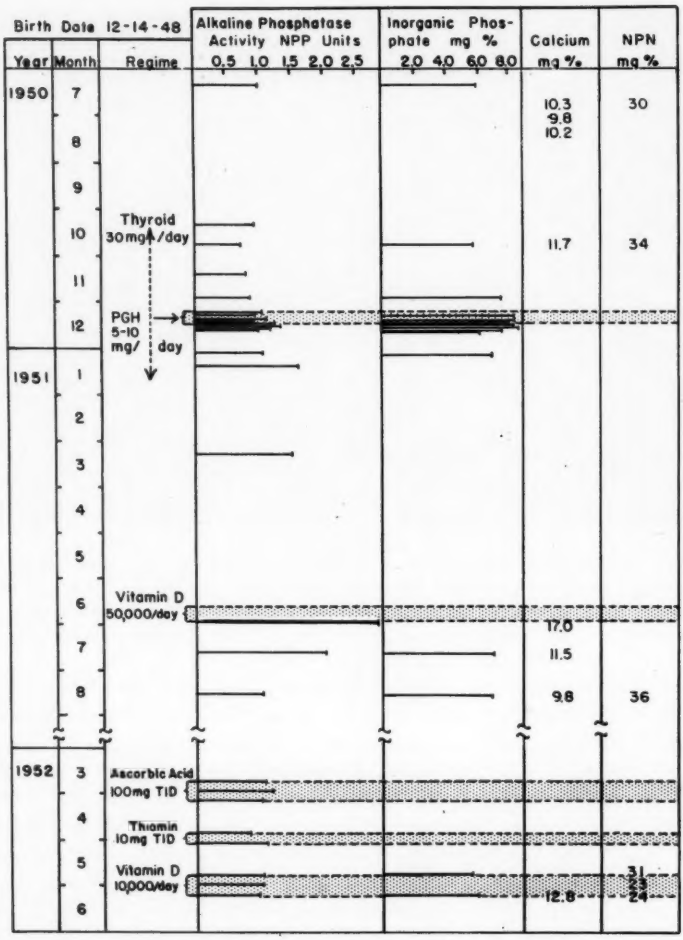

FIG. 6. Summary of laboratory findings and response to therapy. It will be noted that values for plasma alkaline phosphatase activity were consistently low and were not altered by therapy with exception of one determination at completion of 10 days of treatment with vitamin D 50 thousand u. daily.

of benefiting the patient and of casting some light on the underlying metabolic abnormality. The results are summarized in figure 6.

1. Trial of thyroid gland substance USP, 30 mg. daily for 3 mo., was without effect. This was undertaken, despite lack of evidence of thyroid deficiency, because of the effect of thyroid hormone on alkaline phosphatase activity of bone,[25] and because of the synergism of thyroid hormone with pituitary growth hormone in stimulating cartilage growth.[26]

2. Trial of purified growth hormone* failed to influence alkaline phosphatase (Fig. 6). The hormone was given intramuscularly in saline solution 5 mg. daily for 2 days and 10 mg. for 5 days.

* Growth hormone (lyophilized, Lot No. J 21609 R) was provided by Dr. Albert H. Holland of Armour Laboratories. It had approximately 10% TSH activity and was free of ACTH.

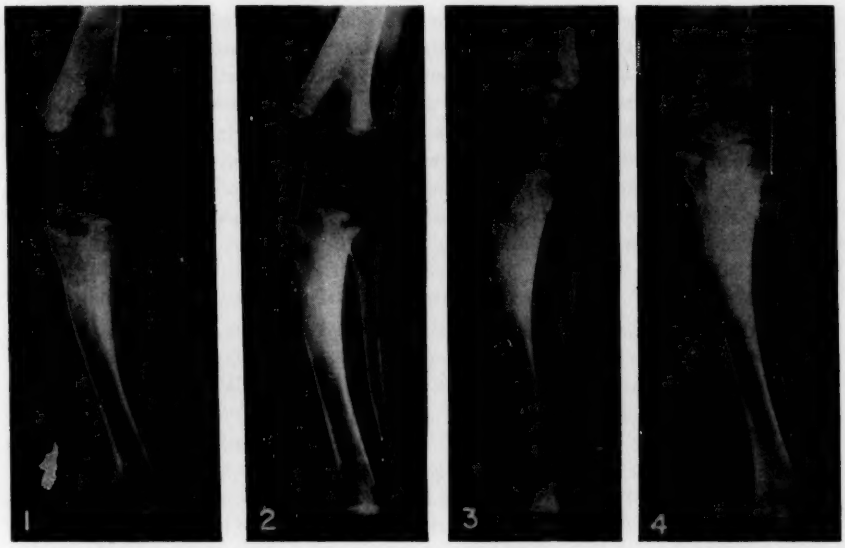

FIG. 7. RGs of L leg, taken at standard tube distance and reproduced to scale. Distinct bone growth is evident. (1) At 22 mo.; (2) at 27 mo.; (3) at 34 mo.; (4) at 41 mo. Arrows indicate transverse lines of increased mineralization, believed to represent effect of vitamin D therapy.

This last represents 1 mg./kg. body weight, and induced anorexia, irritability and a loss of 1 kg. weight. Serum inorganic phosphate rose to 8.4 mg./100 cc. Listlessness, anorexia and nausea have been noted by Lewis, Klein and Wilkins[27] in patients given purified growth hormone. Albright observed an increase in plasma alkaline phosphatase of an adult in response to growth hormone.[28]

3. Trial of vitamin D,† 50 thousand u. daily, had to be discontinued after 10 days of treatment because of development of anorexia and constipation. At this time plasma Ca was 17 mg./100 cc. Alkaline phosphatase had risen to 2.91 NPP u. which was almost triple the amount present before treatment, although it was still abnormally low. Despite hypercalcemia there was no increase in calcium content of urine. Serum Ca and alkaline phosphatase subsequently returned to their control values. Roentgenograms showed a faint line of increased mineral deposition, which is best seen in a film made some months after vitamin D therapy had been discontinued (Fig. 7 [4]). There was no evidence of metastatic calcification. A second course of vitamin D therapy was undertaken 1 yr. later. After 2 wk. of treatment with 10 thousand* u. daily there was a moderate increase in serum Ca, with no change in alkaline phosphatase activity or inorganic phosphate.

4. Although intake of vitamin C was adequate and ascorbic acid content of serum was normal, for 2 wk. ascorbic acid 100 mg. was given orally 3 times daily. This did not influence the plasma alkaline phosphatase activity.

5. A 2 wk. trial was made with thiamin chloride, 10 mg. being given by mouth 3 times daily, because of relationship between thiamin and vitamin D in phosphorylation.[29] There was no change in plasma alkaline phosphatase activity.

PROGRESS OF THE PATIENT

The child has remained in reasonably good health. There has been no hypertension and no evidence of diminished renal function. The serum inorganic phosphate has not

† Vitamin D preparation was ertron® (Whittier Laboratories), activated vaporized ergosterol, 50 thousand USP u./5 mg. capsule.

* Vitamin D preparation was viosterol® in oil (Abbott Laboratories), irradiated ergosterol in sesame oil, 1 gm. equivalent to 10 thousand USP u.

decreased as would be expected, but has remained at normal infantile levels with increasing age. All the deciduous teeth have erupted, but most of them have been shed. Only the deciduous molars seem to be firmly rooted. The skeletal disease continues to be active. Progressive deformities of the thorax and the legs are the most obvious signs. Braces have succeeded in improving the appearance and function of her legs. She has continued to gain in weight and height at a satisfactory rate. Figure 7 shows tracings of roentgenograms of the legs, and demonstrates a distinct increase in the length of the bones. The tongue has exhibited a patchy mottled appearance difficult to describe and varying in extent and location from time to time.

Observations on Similar Patients

Preliminary and incomplete information regarding several children, either seen personally or reported to the authors by others, revealed other instances of the association of deficient alkaline phosphatase activity with a skeletal disorder. Available observations of the alkaline phosphatase activity of these individuals and their families are summarized in table 1. Patient 2 is a 20 month old boy, now being studied, who began to lose deciduous teeth at 18 months. The roentgenograms of his legs were similar to those of the patient who has been described. Abnormally low alkaline phosphatase activity was found in the plasma of this child, his brother and his mother. Patients 3 and 4, siblings, are mentioned by permission of Drs. A. M. Butler, Gertrud C. Reyersbach and Warren Wheeler. Both children died in infancy, having skeletal and renal disease and low plasma alkaline phosphatase activity. Their parents, seen some years later, displayed no skeletal disease, but had low plasma alkaline phosphatase activity; a surviving, healthy child had normal plasma alkaline phosphatase. Dr. Luigi Luzzati kindly provided serum from Patient 5. This is a girl with a skeletal disease reminiscent of severe rickets, manifesting itself when the child was six months old. Her deciduous teeth began to exfoliate shortly after their first eruption when the child was nine months old. The plasma alkaline phosphatase of both parents was abnormally low. Patient 6 is one of four siblings, only one of whom is free of skeletal disease (patients of Dr. S. W. Clausen*). The affected children began to lose teeth at the ages of 12 and 18 months. A paternal cousin of this family may have died of rickets. In none of the families mentioned was there any known disturbance of calcium metabolism. The inorganic phosphate of the serum was moderately elevated in several of the children.

Discussion

It appears evident that the virtual absence of alkaline phosphatase activity in the plasma and biopsied tissues is related to the patient's bone disorder. With the usual stains for undecalcified bone the architecture of the biopsied rib could not be distinguished from that of active rickets. There was abundant osteoid and the osteoblasts appeared as they usually do in rickets. The fact that the alkaline phosphatase activity of the costochondral junction was less than 1/15th that of similar tissue obtained from a child with active rickets and only 1/7th that of two normal children indicates that the patient's osteoblasts must have been nearly free of alkaline phosphatase. It is noteworthy that the child is able to grow well, and that her osteoblasts are able to provide osteoid, even though they are apparently limited in their ability to produce alkaline phosphatase.

* Deceased.

It is generally considered that the alkaline phosphatase activity of plasma reflects osteoblastic activity, since it is highest during the most rapid phases of growth and becomes abnormally elevated when the activity of the osteoblasts is increased in such diseases of bone as rickets and hyperparathyroidism. The normal concentrations of Ca and inorganic phosphate in the patient's serum suggest that the disorder of bone formation is not caused by a primary disturbance in mineral metabolism but is probably related to the local dearth of alkaline phosphatase acitivity. The slight improvement in mineralization which was achieved by the 10 day course of administration of 50 thousand units of vitamin D daily is interpreted as a reflection of the abnormally high level reached by the serum Ca (17 mg./100 cc.), in addition to the three-fold rise in alkaline phosphatase activity. It is remarkable that hypercalcemia developed so rapidly in response to this dose of vitamin D.

The role of alkaline phosphatase activity in the formation of bone is incompletely understood. It is thought to be related in some way to the deposition of mineral salts, possibly by increasing the local concentration of inorganic phosphate as originally set forth by Robison.[30] Meyerhof's observation[31] of transphosphorylation by alkaline phosphatase suggests that the enzyme may play a major role in energy transfer. Gutman and Yü[32] have proposed a concept of the role of phosphorylative glycogenolysis in endochondral calcification and have discussed the possible action of alkaline phosphatase as a dephosphorylating, synthesizing or transphosphorylating agent. The work of Neuman, DiStefano and Mulryan[33, 34] indicates that in the absence of alkaline phosphatase, ester phosphate may be inhibitory to calcification.

Rathbun's observation[9] that his patient displayed low plasma activity coupled with a generalized deficiency of alkaline phosphatase suggests that all the tissues of the present patient may contain as little alkaline phosphatase as those which have been analyzed. It is of interest that there is no sign of dysfunction of any system other than the skeletal and dental, even though the liver has been demonstrated to be relatively lacking in alkaline phosphatase activity. The low alkaline phosphatase of the liver may in part reflect the small amount that is available for excretion in the bile. It is noteworthy that tissues such as skin, kidney, intestine and connective tissues which are known to have a high alkaline phosphatase activity[35–39] are apparently functionally unaffected.

The cause of the enzyme deficiency remains obscure. The low activity does not appear to be due to the presence of an inhibitor, such as beryllium, or to excessive excretion. Low alkaline phosphatase activity has been found in one or both parents in several families having children similarly afflicted. These observations suggest that the disorder may be genetically determined. The basic disturbance may be lack of synthesis of the enzyme, synthesis of an improperly constructed enzyme molecule, or lack of an as yet unknown prosthetic group or activator for this enzyme.

Summary

A child, studied between the ages of 1½ and 3½ years, presented an abnormally low plasma alkaline phosphatase activity (0.8-1.64 Bessey-Lowry u.), a deformed skeleton and the loss of most of her deciduous teeth. The serum Ca was normal; the serum inorganic phosphate remained at the normal relatively high levels of infancy as the child grew older. Roentgenograms demonstrated deficient mineralization of the skeleton and teeth. Biopsies of the liver and the costochondral junction displayed a deficiency of tissue alkaline phosphatase activity. The architecture of the rib was consistent with rickets. There was no

evidence for the presence of an inhibitor of alkaline phosphatase, such as beryllium, or for an excessive excretion of the enzyme. Treatment with purified growth hormone, ascorbic acid and thiamin chloride had no effect, while vitamin D 500 thousand u. caused little change in the enzyme activity in a 10 day period. The father had low plasma alkaline phosphatase activity and a number of similar patients are mentioned, for whom there was also evidence that the deficiency in alkaline phosphatase activity may be genetically determined.

While the precise role of alkaline phosphatase activity in the metabolism of bone is not clear, the findings in this patient suggest that growing bone may require the presence of alkaline phosphatase for normal calcification, and that the skeletal disorder, which could not be distinguished from rickets, may be related to a disturbance in the local factor.

Acknowledgments

Elizabeth Beck performed many of the initial laboratory measurements. Vernet Equipment Foundation of Antioch College loaned the flame photometer used in these studies. Dr. Arthur Lewis served as dental consultant.

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SPANISH ABSTRACT

Deficiencia de la Actividad de la Fosfatasa "Alcalina" Asociada con Raquitismo y Pérdida Prematura de los Dientes, en la Infancia

El artículo presenta los estudios realizados en un niño entre los 1½ y 3½ años de edad que tenía una actividad anormalmente baja de la fosfatasa alcalina del plasma (0.8-1.63 unidades Bessey-Lowry), un esqueleto deformado y pérdida de la mayor parte de sus dientes deciduales. El calcio sérico fué normal, el fosfato inorgánico del suero permaneció en los niveles normales relativamente altos de la infancia a medida que el niño avanzaba en edad. Las radiografías demonstraron mineralización deficiente del esqueleto y de los dientes. Las biopsias del hígado y de la unión costocondral mostraron una deficiencia de la actividad de la fosfatasa alcalina tisural. La arquitectura de la costilla era compatible con raquitismo. No había pruebas de la presencia de algún inhibidor de la fosfatasa alcalina, como el berilium, o de excreción excesiva de la enzima.

El tratamiento con hormona purificada de crecimiento, ácido ascórbico y cloruro de tiamina no tuvo efecto, mientras que 500.000 unidades de vitamina D produjeron un cambio ligero en la actividad de la enzima en un periodo de 10 días.

El padre del enfermo tenía baja actividad de la fosfatasa alcalina plasmática y se mencionan varios enfermos similares en quienes también hubo pruebas de que la deficiencia en la actividad de la fosfatasa alcalina pudiera ser determinada genéticamente.

Aunque no es claro el papel preciso de la actividad de la fosfatasa alcalina en el metabolismo óseo, los hallazgos en este enfermo sugieren que el hueso en crecimiento puede requerir la presencia de fosfatasa alcalina para la calcificación normal y que el trastornos esquelético, que no pudo distinguirse del raquitismo, pueda estar relacionado con una perturbación en el factor local.

Elland Avenue and Bethesda

COMPARISON OF THE THERAPEUTIC EFFICACY OF FOUR AGENTS IN PERTUSSIS

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DURING the past several years a number of therapeutic agents have been reported to be effective *in vitro* and *in vivo* against H. pertussis.[1-22] Each one of these agents has its enthusiastic advocates; on the other hand, there have been few controlled investigations which provide a valid basis for comparison of one agent with another.

This paper presents the results of a study designed to compare the efficacy of four specific treatments for pertussis: streptomycin, chloramphenicol, rabbit antiserum and human serum from immunized donors. It represents the combined efforts of staff of the Babies Hospital, Willard Parker Hospital and the Division of Laboratories and Research, New York State Department of Health.

ORGANIZATION OF STUDY

The difficulties encountered in the evaluation of therapeutic agents in pertussis are well known. Therefore the organization used for collecting data merits description. A resident was assigned to the pertussis ward at Willard Parker Hospital full time, a pediatrician assessed the result of treatment in each patient in the study 3 or 4 times weekly, and a bacteriologist devoted full time to various laboratory aspects. Only patients whose nasopharyngeal cultures showed H. pertussis were included in the analysis. Patients who had received H. pertussis vaccine were excluded from the study.

In order to avoid bias, patients to serve as controls and for each therapeutic agent were chosen by a lottery method. To minimize the variable influence of secondary bacterial invaders (slowly absorbed) procaine penicillin* was given to all patients intramuscularly, once daily for 5 days when therapy was begun, or after 48 hr.' observation in controls. All except three patients studied were less than 24 mo. of age.

During the 1st 9 mo. of the study, which was begun in January 1949, specific treatment was not instituted until H. pertussis had been grown from nasopharyngeal cultures. Subsequently, therapy was applied after observation for 48 hr., and any patients from whom this micro-organism could not be recovered were eliminated from the study. During the observation period, 7 criteria were used to assess the pretreatment status. Daily records were made of the character and frequency of paroxysms, the respiratory rate, amount of vomiting, food intake, weight gain or loss, amount of mucus, and number of white blood cells and the differential count. The character of the paroxysms was designated as mild when they caused no emotional disturbance in the infant, moderate when they were disturbing to the patient but could be handled without help from the nurse, and severe when help was needed even in the prone position.

Change in the course of the disease was judged on the basis of the same criteria. Daily records

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* Procaine penicillin (crysticillin) was supplied by E. R. Squibb & Sons.

were continued throughout. At 6, 10 and 21 days after the beginning of specific treatment or in the case of the controls after entry into the study, the result was listed as a success if 5 of the 7 criteria showed improvement or no change when the disease was very mild initially; the scoring demanded that improvement in the character of the paroxysms be one of the 5 criteria.

Patients exhibiting severe disease were treated as a separate group, B; all of these received one of the specific agents. All others were placed in group A which included a control series. Severe disease was defined as follows: (1) paroxysms leading to inability of the infant when in prone position to respire adequately without help of a nurse, for example, by suctioning or artificial respiration or (2) almost continuous paroxysms leading to mechanical interference with adequate caloric intake or oxygen saturation of the blood.

Selection of Therapeutic Agents and Dosage Schedules

Table 1 lists the treatments used and their dosage and schedule. Two types of hyperimmune human sera, a globulin fraction and a dried whole serum were used; the results were combined because of the small number of patients treated with each type. A vial of each of

TABLE 1

Therapeutic Agents Tested

Agents	Dosage and Schedule	
Streptomycin	40 mg./k. q.d. 8 doses, 5 days	
Chloramphenicol	100 mg./k. q.d. 6 doses, 7 days	
Antipertussis serum		
Human	(1) Globulin fraction (2.5 cc./vial)	10 cc. (4 vials)
	(2) Whole serum lyophilized. Contents of each vial reconstituted to 10 cc.	40 cc. (4 vials)
Rabbit	Under 3 mo.	15 cc.
	3 to 12 mo.	20 cc.
	1 to 3 yr.	30 cc.

the products represents the antibody content of 20 cc. of whole hyperimmune human serum. Therefore, each patient treated with human antibody received an equivalent of 80 cc. of whole hyperimmune serum. The antipertussis rabbit serum was produced and supplied by the Division of Laboratories and Research, New York State Department of Health.

In connection with the choice of antibiotics and the dosage of antisera, experimental studies were carried out. The first study examined the minimal effective concentration and the speed of lethal action of four antibiotics on H. pertussis and H. parapertussis: streptomycin, polymyxin B, aureomycin and chloramphenicol* (chloromycetin®). The data which led to the selection of streptomycin and chloramphenicol for clinical trial have been published.[23] Chloramphenicol is less irritating to the gastrointestinal tract and more stable than aureomycin. It was chosen for these reasons rather than for its superiority *in vitro*, though the speed of its lethal action was found to be greater than that of aureomycin. All these agents, in concentrations easily attained clinically, exhibit a significant bactericidal

* Chloramphenicol was supplied by Parke, Davis & Company.

effect on small populations and completely prevent the growth of approximately 1,000,000 bacterial cells seeded in a 2 mm. loopful of broth on the surface of antibiotic containing agar; this was subsequently shown to be true for terramycin also.

In the second study a factual basis was sought for choosing the required volume of a given therapeutic serum. The clinical study was begun before accurate means of measuring the efficacy of the available sera had been devised. Therefore, the authors relied on the experience of others in selecting the total dosage to be administered; this has customarily been measured in terms of volume. The entire dose of antiserum was given at one time. A quantitative approach is essential for evaluation of a therapeutic antiserum, and two requirements are necessary to attain this end: (1) a quantitative measurement of the concentration of antibody in the serum and (2) a test for determining the adequacy of the dosage in each individual case.

Measurement of antibody nitrogen/cc. in the therapeutic rabbit serum and in human antisera by a quantitative agglutinin method was used to satisfy the first requirement.[24] The quantity of rabbit antibody administered was 4 to 6 times larger than the amount of antibody in the selected dose of human serum (table 1). It is of interest to compare the antibody content of available pertussis therapeutic antisera. A gamma globulin fraction from hyperimmune human serum, concentrated 10 or more times by volume, contained 1.0 mg. agglutinin nitrogen/cc. Another human serum in lyophilized form reconstituted to 10 cc. with distilled water contained 0.32 mg./cc. The New York State rabbit antiserum with a volume concentration of from 6- to 8-fold contained 2 to 4 mg./cc.

Does this quantitative chemical method measure protective antibody? By means of the intracerebral mouse protection test, Dr. Pearl Kendrick has shown in collaboration with the present authors that removal of antibody by absorption with H. pertussis, as shown by measurement of agglutinin nitrogen, also removed the protective power. However it was not possible to show a direct correlation between the agglutinin nitrogen content and the degree of mouse protective power.[25] The results of repeated mouse protection tests of the same serum varied too widely to permit an evaluation of the agglutinin nitrogen as an index of protective potency.

The second requirement was met by measuring the excess of antibody in the serum of patients after administration of human or rabbit antiserum in the dosage indicated. In patients receiving rabbit antiserum, the sera showed excess of antibody when diluted to 1:1000 or greater, whereas the titres of sera from those treated with human antiserum ranged from 1:8 to 1:64.[26] The doses of human and rabbit antibody used in this study are those in general use. If agglutinin nitrogen measures the curative antibody, the study does not offer a valid comparison between the two kinds of antisera.

Evaluation of Therapeutic Efficacy in Group A

The efficacy of any treatment in pertussis may be influenced by three factors, age of patient, severity of infection and duration of disease. By chance these possible influences were well distributed among the therapeutic groups and controls in this study with two exceptions; in the group treated with human sera, there was a higher proportion of young infants and of infections of moderate severity (table 2). Most important is the fact that only 30% of the patients were treated within 10 days of the onset of cough, probably 2 or 3 weeks after the start of their infections; 61% were treated within 15 days of onset of cough or after at least three weeks of infection. On the other hand, 26% of all the patients were 3 months of age or less and 53% were under 6 months of age.

TABLE 2

FACTORS WHICH MAY INFLUENCE EFFECT OF THERAPY

Therapeutic Agents	Total Pts.	Severity of Infection				Age of Patient				Cough Duration			
		Mild		Moderate		3 mo. or less		6 mo. or less		10 days or less		15 days or less	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Controls	45	37	82	8	18	12	26	26	58	17	38	33	73
SM	66	50	76	16	24	15	23	33	50	18	27	33	50
HS	27	16	59	11	41	12	45	19	70	4	15	20	74
RS	55*	43	78	12	21	14	25	26	47	16	29	33	60
CM	49	37	77	12	24	11	22	24	49	19	38	29	59

SM = Streptomycin
HS = Human antiserum
RS = Rabbit antiserum
CM = Chloramphenicol

* Five additional patients were treated with rabbit antiserum in single 5 cc. dose. One was less than 3 mo., 2 under 6 mo. of age. One was coughing less than 10 days and 2 for less than 15 days when treated.

Assuming that the stage of disease must play an important role in influencing results of any treatment, analysis of the therapeutic results has been made according to duration of cough at the start of treatment. Table 3 shows the evaluation of all four therapeutic regimens and the controls six days after start of specific treatment or observation. When all patients are included three of the agents show fewer failures than the controls but the differences are not convincingly significant. The data based on response of patients treated within 15 days of onset of cough indicate a slightly higher percentage of failures among the controls and with two of the agents. Chloramphenicol is the only agent with a considerably reduced rate of failure in patients who were treated within 10 days of onset of cough.

Similar data compiled from results 10 days after the beginning of treatment are presented in table 4. When all patients are included, all agents appear better than the controls

TABLE 3

PATIENTS SHOWING FAILURE UNDER 5 THERAPEUTIC REGIMENS AT 6 DAY INTERVAL

Influence of Duration of Cough

Therapeutic Agents	Duration of Cough								
	Patients			15 days or less			10 days or less		
	Total Pts	Failures No.	%	Total Pts	Failures No.	%	Total Pts	Failures No.	%
Controls	45	23	51	34	19	56	23	14	61
Streptomycin	66	28	42	33	17	52	18	9	50
Human antiserum	27	14	52	20	13	65	4	2	50
Rabbit antiserum	55*	23	42	33	14	42	16	8	50
Chloramphenicol	49	17	34	29	8	27	19	6	32

* Five patients treated with only single dose of 5 cc. of rabbit antiserum all scored success.

TABLE 4

PATIENTS SHOWING FAILURE UNDER 5 THERAPEUTIC REGIMENS AT 10 DAY INTERVAL

Influence of Duration of Cough

Therapeutic Agents	Duration of Cough								
	Patients			15 days or less			10 days or less		
	Total Pts	Failures No.	%	Total Pts	Failures No.	%	Total Pts	Failures No.	%
Controls	45	16	36	34	11	32	23	10	43
Streptomycin	66	12	18	33	7	22	18	5	28
Human antiserum	27	4	15	20	2	10	4	0	0
Rabbit antiserum	55*	11	20	33	5	15	16	2	12
Chloramphenicol	49	10	20	20	7	24	19	7	37

* Of 5 patients treated only with single 5 cc. dose only one scored failure.

but there is no difference among them. In patients treated within 15 days of the onset of cough, the two antisera were the most effective. The statistical significance of the difference between the control group and each of the therapeutic groups was calculated. Only the two kinds of antisera proved to be significantly better than the control group when the total number of patients were analyzed, $p = 0.02$ for human serum and $p = 0.02$ for rabbit antiserum. When the groups were divided into early and late cases the smaller numbers made the differences less significant.

Table 5 shows evaluation 21 days after start of treatment. It is seen that only approximately 25% of the controls have been scored as failures. Any therapeutic agent which is clearly superior should show no failure at 21 days. This was true only for the early cases treated with human serum but there are only four such cases. Moreover even in the earliest group treated, most patients had had the infection for six weeks when the 21 days' assessment was made. While the 21 days' result was not scored as a success unless the disturbing symptoms of pertussis had disappeared, absence of the cough was rare.

TABLE 5

PATIENTS SHOWING FAILURE UNDER 5 THERAPEUTIC REGIMENS AT 21 DAY INTERVAL

Influence of Duration of Cough

Therapeutic Agents	Duration of Cough								
	Patients			15 days or less			10 days or less		
	Total Pts	Failures No.	%	Total Pts	Failures No.	%	Total Pts	Failures No.	%
Controls	45	10	22	34	8	24	23	6	26
Streptomycin	66	8	12	33	4	12	18	3	17
Human antiserum	27	2	7	20	1	5	4	0	0
Rabbit antiserum	55*	8	14	33	5	15	16	2	12
Chloramphenicol	49	6	20	29	5	17	19	4	21

* Of 5 patients treated with single 5 cc. dose of rabbit antiserum all scored success.

TABLE 6

COMPARISON OF RESULTS OF SCORING BY 7 CRITERIA WITH THOSE BASED ON GENERAL CLINICAL IMPROVEMENT

Patients Showing Failure at 6 Days

	According to 7 Criteria			According to Clinical Evaluation		
	Total Pts.	Failures No.	%	Total Pts.	Failures No.	%
Controls	45	23	51	39	17	43
Streptomycin	66	28	42	66	20	30
Human antiserum	27	14	52	24	11	45
Rabbit antiserum	55*	23	42	54	17	31
Chloramphenicol	49	17	34	45	10	22

Patients Showing Failure at 10 Days

	According to 7 Criteria			According to Clinical Evaluation		
	Total Pts.	Failures No.	%	Total Pts.	Failures No.	%
Controls	45	16	36	39	5	12
Streptomycin	66	12	18	65	6	9
Human antiserum	27	4	15	23	1	4
Rabbit antiserum	55*	11	20	52	7	13
Chloramphenicol	49	10	20	45	4	9

* Five patients were treated with only single 5 cc. dose of rabbit antiserum. All were scored success at 6 days. At 10 days according to 7 criteria, 4 of 5 scored success.

TABLE 7

GROUP B—SEVERE INFECTIONS

Therapeutic Agents	Total Pts.	Evaluation of Therapeutic Regimens: Failures at Intervals After Therapy					
		6 Days		10 Days		21 Days	
		No.	%	No.	%	No.	%
Control							
Streptomycin	4	4	100	1	25	2	50
Human antiserum	5	4	80	3	60	2	40
Rabbit antiserum	3	2	66	1	33	1	33
Chloramphenicol	1	1	—	0	—	0	—

The response of the patients in group A was also evaluated on the basis of general clinical improvement. The results are shown in table 6. The number of failures on this basis was less in all groups, treated and control, but the relative values for the different groups showed no real differences from those obtained by assessment on the basis of the seven specified criteria.

Evaluation of Therapeutic Efficacy in Group B

The number of patients with severe infections (group B) was too small for comparison of the efficacy of these treatments but the limitations of each agent were apparent (table 7). Three patients in the control group were transferred to group B and received specific therapy because of the progression of their disease to its severe form.

Group B consisted of 13 patients; 5 were under 3 months of age and 8 were less than 6 months old. Eight patients were admitted with a history of cough for 7 days or less. Only 2 patients were scored as successes after 6 days of therapy. None were severely ill after 10 days, although they could not be called successes according to the authors' criteria. According to the clinical evaluation of these patients after 10 and 21 days of therapy, there was marked improvement.

Analysis of Deaths Which Occurred During the Study

There was only one fatality related to pertussis in the patients included in this study. This occurred in an 11 month old girl who was admitted with a four day history of moderate cough, no vomiting and a sudden onset of convulsions, lethargy and finally coma. She never regained consciousness and remained hypertonic and opisthotonic. Her cough remained mild but she developed signs of widespread consolidation throughout both lungs.

Another fatality occurred in a 7 week old baby who was scheduled to be included in the study. Death occurred suddenly and unexpectedly 36 hours after admission during the period of observation before any therapy was given. He had appeared as a well baby except during paroxysms which he handled without any difficulty. His physical examination had been negative. Postmortem examination was not performed.

Two other patients in this study died soon after they had successfully recovered from pertussis. One was discharged after 24 days in the hospital at which time she had completely recovered from a mild pertussis. She was readmitted in two weeks with signs and symptoms of bronchitis. She ran a low grade fever for 2 weeks and was only mildly ill. Nevertheless chest roentgenogram showed atelectasis of a large part of the right lung which persisted for two months. Her tuberculin skin test, which had been negative in her first admission, had become positive. She was bronchoscoped and died 24 hours later. Postmortem examination showed miliary tuberculosis. The second patient developed severe diarrhea just as he was ready for discharge after recovering from moderate pertussis. He died after several bouts of severe diarrhea and acidosis. No postmortem examination was made.

There were four other deaths from H. pertussis in 1,151 admissions at Willard Parker Hospital during the period of this study. One patient was six weeks old and had been coughing for 2¼ weeks. On admission she had already received pertussis vaccine, human antiserum, sulfadiazine and streptomycin and therefore was not admitted to the study. She was severely ill with widespread pneumonia on admission and was given rabbit antiserum and streptomycin. She improved in 10 days and was able to take feedings and

had few moderate paroxysms. She developed pneumonia again after three weeks and died suddenly. At postmortem examination, H. influenzae was cultured from the lungs and inclusion bodies were noted in the lungs and liver. One child in whom there was no suspicion of pertussis was admitted with a clinical diagnosis of meningitis. At postmortem examination less than 24 hours after admission cultures from the lungs showed H. pertussis. Two other patients on admission showed convulsions, clinical signs of meningeal irritation, depression of the sensorium and mild cough. Both had received numerous antibiotics before admission and were therefore not admitted to the study. Pertussis was suspected in one because of a two week history of cough and some vomiting. Both died with marked encephalopathy. Their cultures were positive for H. pertussis. Both of these patients and the patient with encephalitis included in this study had histories of only moderate cough and occasional vomiting.

Results of Combined Serum and Antibiotic Therapy

Eight patients were treated with both rabbit antiserum and chloramphenicol in the dosage schedule described. Three had been coughing for three weeks or more and were already recovering from their illness. Four others had an extremely mild disease so that recovery was difficult to evaluate. When these patients were scored as success or failure on the basis of the seven criteria the incidence of failures was lower than in the controls and other therapeutic groups, but as in these latter groups, prompt elimination of the symptoms and signs of pertussis did not occur.

By chance, the treatment of a pair of twins who had diseases of similar severity provided a good experimental comparison. The first received rabbit antiserum and chloramphenicol, the second was a control.

J. A. B., a 3 mo. old twin, was admitted to Willard Parker Hospital with a history of coughing for 2 wk. and occasional vomiting. Birth weight was 0.9 kg. He had gained steadily and at time of admission weighed 3.3 kg. He had been exposed to a sibling who had pertussis. Physical examination on admission revealed a well developed, fairly well nourished and well hydrated infant in no distress who had mild and moderate paroxysms. There was some mucus present in nasopharynx. Eyes were slightly puffy. Respiratory rate was slightly elevated (50 to 60/min.) at rest. There was some dyspnea and fatigue immediately following paroxysms. Bilateral harsh moist rales could be heard at both lung bases. No other abnormalities were evident. During first week in the hospital, patient's caloric intake was fair and there was very little vomiting. Paroxysms increased in number and severity and suctioning was occasionally necessary, nevertheless he did not look sick between paroxysms. He remained afebrile throughout his disease. On 2nd hospital day he received penicillin, rabbit antiserum 20 cc. and chloramphenicol, 100 mg./kg., which was to be continued for 7 days. Six days after therapy was begun cough was less frequent and severe. Patient was more alert and responsive. Appetite had improved and he had gained 0.25 kg. Respiratory rate was normal and lungs were clear on physical examination. Ten days after onset of therapy paroxysms were mild and infrequent and patient had continued to gain weight. Physical examination showed no abnormalities. The patient continued to improve and 21 days after onset of therapy he had a short paroxysm occasionally but was otherwise well.

Four days after admission of J. A. B., his twin, J. Al. B., was admitted to Willard Parker Hospital. Their histories were identical. The family had planned to care for one of the babies at home but during this 3rd wk. of coughing he had become cyanotic and exhausted after an occasional prolonged paroxysm. By chance he was placed in the control group and received penicillin alone. He appeared to be a little more irritable and fatigued than his brother. Respirations were rapid, 65/min., and somewhat labored. Color was good and there was a moderate amount of mucus in nasopharynx. Coarse rales, which cleared after a paroxysm, were heard throughout both lungs. He handled his paroxysms well but was somewhat listless after prolonged coughing. Six days after admission, which was 10 days after his brother's admission, patient was markedly improved and looked as well as his

brother. Paroxysms were milder and less frequent, appetite was good, he had gained weight and was alert and playful. Physical examination was entirely negative. Hospital course could not be said to be any different from that of his brother.

Influence of Therapeutic Agents on Persistence of H. Pertussis in Nasopharynx

In contrast to the clinical observations, bacteriologic data indicated marked differences in the capacities of the four therapeutic agents to eliminate H. pertussis from the nasopharynx. The data were based on the isolation of H. pertussis from cultures taken at various intervals after the initiation of therapy or, in case of controls, after entry into the study.

Nasopharyngeal mucus was obtained by means of special applicators on flexible copper wire which were passed through the nares to the posterior pharyngeal wall and kept in place for approximately 15 sec. The mucus-laden swab was put in a tube containing broth 0.2 cc. and sent to the laboratory. Culture media were inoculated as soon as possible, always within 2 hours from the time of collection. Plates of a modified Bordet-Gengou agar which contained penicillin 0.5 u./cc. were seeded by streaking half of the plate with the swab; a loop was then used to spread the inoculum to the second half of the plate.

TABLE 8

Isolation of H. Pertussis from Treated Group A Patients

Results with Single Cultures

Treatment	Days after Start of Therapy					
	7 or less			More than 7		
	Total Patients	H. pert. recovered		Total Patients	H. pert. recovered	
	No.	No. Pts.	%	No.	No. Pts.	%
Control	11	8	72.7	15	7	46.6
Streptomycin	44	23	52.2	51	23	45.2
Chloramphenicol	25	8	32.0	30	7	23.3
Human serum	9	4	44.4	9	2	22.2
Rabbit serum	33	4	12.1	36	3	8.3

Results with Multiple Cultures

	Days after Start of Therapy					
	7 or less			More than 7		
	Total Patients	H. pert. recovered		Total Patients	H. pert. recovered	
	No.	No. Pts.	%	No.	No. Pts.	%
Control	26	21	80.5	26	14	53.8
Streptomycin	15	12	80.0	15	9	60.0
Chloramphenicol	18	8	44.4	19	6	31.5
Human serum	16	13	81.2	15	10	66.6
Rabbit serum	17	9	52.9	17	2	11.8

Isolated colonies did not usually appear until after 4 or 5 days of incubation but where heavily seeded, confluent growth could frequently be seen in 48 hours. Preliminary identification of H. pertussis was based on cultural and morphologic characters and the results of slide agglutination tests with normal rabbit, antipertussis and antiparapertussis sera. Confirmatory tests were later made by tube agglutination titrations.[27]

There were two series of observations. In the first nine months of the study, although 3 or 4 cultures were taken prior to treatment, single swab cultures were taken at given intervals following therapy. In the last nine months of the study, four swab cultures were examined at each interval subsequent to treatment. In the second series, the isolation of H. pertussis was more frequent in all groups, illustrating the advantage of multiple cultures. In both, however, the antipertussis rabbit serum which was given in one dose was more effective in reducing the frequency and period of recovery of H. pertussis from the nasopharynx than the other methods of therapy (table 8). Chloramphenicol was also effective but less so even though administration of this drug was continued for seven days. Streptomycin and human serum had little or no effect. The difference in dosage of specific pertussis antibody of human and rabbit origin precludes comparison of the two types of antibody, but the dose of human serum in general use did not appear to affect the isolation of H. pertussis.

Influence of Therapeutic Agents on the White Blood Cell Count

The change in the total white blood cell count has also been analyzed as an index of influence of each form of therapy.

In chart 1 the total leucocyte counts are graphed against the number of days after the onset of cough. Each point represents the average of the counts for each group at

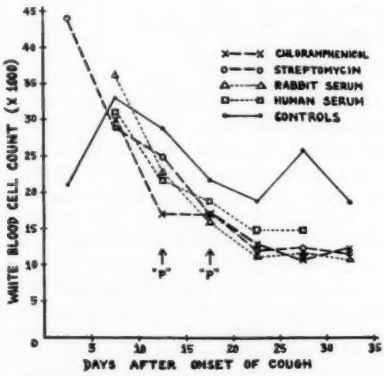

Chart 1. Influence of therapeutic agents on white blood cell counts.

5 day intervals. Total white cell counts of patients who received therapy within 10 days of the onset of their cough and whose initial counts were 20.0 thousand or higher are included in this analysis. Comparison of certain points on the curve of the control group with corresponding points of the therapeutic groups is summarized in table 9. The P values listed indicate the probability that the difference between the two points compared at

TABLE 9

PROBABILITY VALUES OBTAINED ON ANALYSIS OF THERAPEUTIC EFFECTS ON WHITE BLOOD CELL COUNTS

Groups	Period After Onset of Cough			
	11 to 15 Days		16 to 20 Days	
	No. of Cases	"P"*	No. of Cases	"P"
Control:	11		9	
Streptomycin	14	0.20	7	0.15
Chloramphenicol	8	0.01	8	0.15
Rabbit serum	9	0.08	20	0.03
Human serum	8	0.03	5	0.35
Streptomycin, Chloramphenicol, Rabbit serum			35	0.02

* See intervals on chart 1.

P values listed indicate probability that difference between 2 points compared at any time interval is due to chance rather than significant influence of therapy.

any time interval is due to chance rather than a significant influence of therapy. When P was greater than 0.05 the difference between the groups was not considered significant. Chloramphenicol and human serum at 11 to 15 days and only rabbit serum at 16 to 20 days appear to have values significantly different from the control group.

The small numbers of white cell counts from which the averages were determined undoubtedly influenced the magnitude of the P values. This was thought to be especially true of those obtained from the groups treated with chloramphenicol or human serum at 16 to 20 days. When the average of the white cell counts from three therapeutic groups (chloramphenicol, streptomycin and rabbit serum) is treated as one group of 35 cases and is compared with the control group at 16 to 20 days, the P value falls to 0.02.

The results obtained at the 25 to 30 days interval were not analyzed because it was felt that influence of therapy on the white blood cell count in H. pertussis infection should be demonstrable within 7 to 10 days after start of treatment. The increase in the white cell counts in the controls at the interval 20 to 25 days is surprising; evidence for influence of secondary bacterial invaders was looked for but was not found. However, the laboratory studies were not adequate to clarify this point. Even though the numbers of patients contributing to the analysis are small, the consistency with which lower white blood cell counts were found in all therapeutic groups throughout the period of observation leads us to the conclusion that all the therapeutic agents showed some influence on the infection.

DISCUSSION

Prompt elimination of symptoms of pertussis could not be demonstrated with any of the agents tested, but it is possible that their influence might have been much greater if used early in the course of the disease. The majority of the patients had had a paroxysmal cough for longer than 15 days and therefore had presumably been suffering from the in-

fection for over 4 weeks. There is reason to believe that after sufficient damage to the cells of the mucous membrane has occurred, time is required for healing even when the organism has been eliminated. The hypothesis is advanced that prompt recovery from pertussis can be anticipated only when effective treatment is instituted before this damage occurs; it may be that the damage has occurred in most patients by the time the typical paroxysms occur.

Evidence on the influence of the agents on the activity of the H. pertussis infection has been obtained from a study of nasopharyngeal cultures of H. pertussis and the change in the total white blood cell count following treatment. From both sources it must be concluded that rabbit antiserum and chloramphenicol are superior to the others. These data suggest the correctness of the hypothesis that the authors' failure to show clinical signs of prompt recovery is due to the presence in most patients of cellular damage requiring time for restoration of normal function.

When secondary infections are prevented by prophylactic therapy or eradicated promptly by the numerous antibiotics now available, pertussis has proved to be a mild disease in the great majority of patients. The advent of antibiotics has been correlated with diminution of mortality rate in this disease. When the deaths from pertussis which occurred during the period that this study was in progress are examined, we find that 4 out of 8 followed convulsions, coma, and signs of severe brain damage. This experience indicates the need for investigation of the nature and pathogenesis of the cerebral injury. At present there are no data to determine whether this lesion results from anoxia, from chemical changes secondary to hyperventilation, or is the result of true encephalitis.

When these results are viewed as a whole the conclusion is inescapable and is in line with the clinical impression of those who observed these babies at frequent intervals: significant difference in therapeutic efficacy among the four treatments has not been demonstrated. Moreover, a careful comparison of the results in the control group, who received only penicillin, with those in infants receiving specific treatments has not established a convincing difference.

In the meantime, until proof is available for the hypothesis offered, how shall patients with pertussis be treated? Even though the data do not prove that the specific agents studied bring about prompt recovery, they suggest that all of them influence the course to some degree. If we assume that on clinical evidence there are no significant differences in efficacy among the four different agents in this study, a selection will be influenced by toxicity, ease of administration and cost of the therapeutic agents.

A number of reports suggest that chloramphenicol may injure the hemopoietic system. An occasional patient has developed aplastic anemia in association with administration of chloramphenicol. Most of these patients exhibited various forms of allergy and received the antibiotic for extended periods or repeated frequently. There was no evidence of injury in any of the patients in this series.

Serum reactions beginning from 6 to 16 days after the injection of serum were recorded on the clinical summaries of 17 (28.3%) of the 60 rabbit-serum treated cases. In 10 cases, there was erythema or urticaria, or both, accompanied by elevated temperatures; in 4 of these the temperature was 39.4°C. or more; in one, ("serum sickness severe") erythema lasted for 11 days and the febrile reactions of from 38.4°C. to 40.2°C. for 8 days; and in another, there was a "severe rash" persisting for 3 weeks and temperatures ranging up to 39.9°C. for 6 days. In 6 other cases, the reactions were limited to urticaria, erythema, or "rash" of from 1 to 4 days' duration. In the 17th case, there was only a slight temperature

rise (37.9°C.). In addition, among cases in which serum reactions as such were not recorded, there were seven in which elevated temperatures, beginning from 6 to 16 days after serum injection, might possibly be attributed to the serum.

No evidence of toxicity to streptomycin was recognized; however, no vestibular function tests were performed. Experience of the past suggests that no injury would be expected with this dosage intramuscularly for five days unless dehydration or other factors reduced excretion of the streptomycin.

When the three agents used are compared for toxicity, ease of administration and expense, chloramphenicol would stand first. If this agent is instituted early in the course of the disease, there should be no need for another agent to control secondary invaders. In sick infants penicillin is recommended in addition. The importance of nursing care, oxygen and suction when indicated deserves emphasis.

Summary

The results of the study suggest that H. pertussis infection is usually a mild disease in all age groups if there is effective control of most secondary bacterial infections by penicillin. Not one of the four therapeutic agents studied, streptomycin, chloramphenicol, antipertussis rabbit serum and hyperimmune human serum, was shown to bring about prompt elimination of the signs of pertussis. On the basis of duration of the infection in the patients studied, however, only 30% were suitable clinical material for comparing therapeutic agents in pertussis.

The hypothesis is advanced that prompt recovery from pertussis can be anticipated only when effective therapy is instituted early in the course of the disease; the preparoxysmal stage is recommended.

While the data failed to show convincing therapeutic value of any of the four specific agents tested, they suggested some modification by each. A significant difference in degree of influence among the four treatments was not demonstrated. On the basis of toxicity, ease of administration and cost, chloramphenicol is for the present the agent of choice.

In a comparison of the capacity of the four treatments to eliminate H. pertussis from the nasopharynx, rabbit antiserum was best and chloramphenicol next.

All four specific therapeutic agents showed some influence on the characteristic response in the white blood cell count.

Acknowledgment

It is a pleasure to acknowledge the technical assistance of Miss Ruth Schaefer, of the Division of Laboratories and Research, New York State Department of Health.

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SPANISH ABSTRACT

Comparación de la Eficiencia Terapéutica de Cuatro Agentes en la Tosferina

Durante los últimos años se ha reportado que cierto número de agentes terapéuticos son efectivos in vitro e in vivo contra el hemophilus pertussis, cada uno de estos agentes han tenido entusiastas advocadores pero han sido pocas las investigaciones controladas que sustenten bases sólidas para comparar un agente con otro.

Este trabajo presenta los resultados de un estudio hecho especialmente para comparar la eficacia de cuatro tratamientos específicos para la tosferina: estreptomicina, cloranfenicol, suero antitosferinoso de conejo y suero humano de donadores immunizados contra la tosferina.

Los resultados obtenidos por los autores sugieren que la infección por hemophilus pertussis es generalmente una enfermedad moderada en todas las edades si se hace un control efectivo con penicilina de la mayor parte de las infecciones bacterianas secundarias. Ninguno de los cuatro agentes

terapéuticos estudiados; estreptomicina, cloramfenicol, suero antitosferinoso de conejo, y suero humano hiperinmune, produjo la eliminación rápida de los signos de la tosferina. Sin embargo, tomando como base la duración de la infección en los pacientes estudiados, sólo el 30 porciento fueron material clínico apropiado para comparar los agentes terapéuticos empleados.

Se adelanta la hipótesis de que la pronta recuperación en la tosferina puede anticiparse sólo cuando se instituye terapéutica efectiva temprana en el curso de la enfermedad recomendándose para ello el periodo preparoxístico.

Aunque los datos no muestran un valor terapéutico convincente para ninguno de los cuatro agentes específicos probados, sí sugieren que cada uno produce cierta modificacíon. No se demostró una diferencia significante en su grado de influencia entre los cuatro tratamientos. El coramfenicol es por el momento el agente de elección basándose en su toxicidad, facilidad de administración y costo.

Comparando la capacidad de los cuatro tratamientos para eliminar de la nasofaringe el hemophilus pertussis, el antisuero de conejo fué el mejor y en seguida el cloramfenicol.

Los cuatro agentes terapéuticos específicos mostraron cierta influencia sobre la respuesta característica de la cuenta de glóbulos blancos.

622 West 168th Street

ACUTE NICOTINE POISONING

Case Report

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THIS paper reports a case of acute nicotine poisoning in a 2½ year old child and discusses the pharmacology and treatment of nicotine poisoning in man.

Many cases of acute nicotine poisoning in infants and preschool children have been reported. The source of the poison in children is usually tobacco; in adults, it is usually salts of the alkaloid which are common ingredients of insecticides. The incidence of nicotine poisoning appears to be increasing. Franke and Thomas[1] report that McNally found five cases of fatal poisoning in a two year period in Cook County, Illinois, and they found four cases in St. Louis during a 10 year period.

The free base of nicotine is a liquid and is highly soluble in water. Its salts, for example the sulfate, is a crystalline solid and are used in dusting powder by horticulturists and others.[2] The pharmacologic action of nicotine is upon the autonomic ganglia,[3] the postsynaptic neurones which are stimulated at first and later fail to respond to the chemical mediator acetylcholine. These effects on the autonomic ganglia are relatively unimportant though they undoubtedly may cause severe symptoms in man. Nicotine is likely to prove paralyzing through its effect on the peripheral action on the neuromuscular junction which may cause complete failure of respiration.[4] The peripheral skeletal muscle paralysis does not affect all muscle groups simultaneously or equally. The intercostal muscles fail before the diaphragm. Rapid administration of large doses of nicotine may cause death within a minute or less. There is a cardiovascular collapse and a simultaneous respiratory failure, probably of central origin. In accidental poisoning, this type of death is rarely seen, except when a large amount of nicotine is swallowed with suicidal intent. Usually, the onset is gradual with salivation, nausea, vomiting and constriction of the arterioles in the skin due to the release of adrenaline or an adrenaline-like substance. These symptoms are not particularly dangerous and complete paralysis of all autonomic ganglia would not necessarily prove fatal. During systemic poisoning, complete ganglionic block is said not to occur. The danger is the curare-like action of nicotine at the neuromyal junction.

There are, in addition, complex effects upon the cardiovascular system. These effects are the result of the initial release of adrenalin or an adrenalin-like substance. This causes constriction of the arterioles and a rise in blood pressure. There is, simultaneously, a stimulation of both cholinergic and adrenergic postganglionic autonomic neurones. Later, there is a fall in blood pressure, in severe cases, to a very low level; then death is imminent due to shock.

Absorption of nicotine from the gastrointestinal tract is rapid. According to Ganz, Kelsey and Geiling,[5] who used radioactive nicotine, the kidney excretes about 40% of the injected radioactive poison within 3 hours, 85% in 6 hours and almost all within

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16 hours. Approximately 25% is excreted as unchanged nicotine. These data are from the rat. Comparable quantitative data from man are not available, and there is considerable confusion in the earlier literature with regard to the amount of nicotine excreted in the urine.[6] There is general agreement that the liver is capable of destroying nicotine, and this is said to be due to an enzymatic action.[7] Geiling and his coworkers[5] found a relatively high concentration in the liver of experimentally poisoned animals and much lower concentration in muscle.

There are no irreversible tissue changes brought about by acute nicotine poisoning; Franke and Thomas[1] state that provided respiration is supported and cardiovascular collapse is avoided, the nicotine will be partly destroyed, the remainder eliminated in the urine and complete recovery will be prompt. When the systolic blood pressure falls to about 80 mm.Hg renal filtration ceases. With poisons such as nicotine which are largely eliminated by the kidney, the importance of the restoration of the blood pressure is obvious.

Case Summary

A 2¾ yr. old white male child was apparently well and healthy on the morning of admission to hospital. He had complained previously of itching around the anus. While the parents were at work, the grandmother decided that the child should be treated for worms. She had never seen worms in the stool but followed the prescribed treatment of a friend. She steeped a half package of Bull Durham tobacco in a cup of water. She administered this infusion rectally to the child as a warm enema. Within 15 min. after the enema was given the child foamed at the mouth, vomited, and had generalized grand mal type convulsive seizures. Following this he became limp, gritted his teeth, and fell on the floor. Patient was immediately taken to the hospital.

Physical examination revealed a well developed, well nourished male child who was in acute distress with grunting, diaphragmatic-type respirations. Muscles were hypotonic and flaccid. He was pale and unresponsive. Eyes were deflected upward, pupils were dilated, reacting to light directly and consensually. Mouth: a mild infection of pharynx, mucous membranes appeared pale. Chest: there was an intercostal muscle paralysis noted with diaphragmatic breathing. Heart tones were relatively weak, pulse thready and blood pressure was not obtainable. Pulse was 66 mm. and irregular at time of first examination. Reflexes: Triceps, biceps, knee and ankle jerks were diminished.

Treatment: Oxygen was administered through a mask; an intravenous infusion of 2½% glucose and half-strength Ringer's solution was administered, first by "pressure" infusion and later by "drip" infusion. Calcium gluconate 1.0 gm. in 10% glucose was administered intravenously. Caffeine sodium benzoate 0.22 gm. was given immediately, repeated in 2 hr. and in 4 hr. and again 4 hr. later. Pulse increased from irregular, thready at 66 mm. to 84 to 96 mm. within 5 hr. Blood pressure rose to 80/0 mm.Hg, then to 108/60 mm.Hg within 3 hr. This level was then maintained.

Progress: The child continued to improve. By the next morning, he was responsive. Food was well tolerated; administration of intravenous fluid was continued for 12 hr., oxygen was discontinued. Intercostal muscle paralysis disappeared in 18 hr. One week later physical findings were normal locally and neurologically.

Discussion

The acuteness of the child's collapse and extreme shocklike state within a short time emphasizes the speed of action of nicotine. The vasomotor collapse and intercostal paralysis are the more dangerous toxic actions of this poison.

The complete recovery of the patient within a short time indicates the acute temporary nature of the problem. The lack of a specific antidote for severe nicotine poisoning necessitates early recognition and adequate supportive care of the patient.

In this case, an attempt was made to support circulation by the intravenous administration of fluids by "pressure" and later by "drip." The respiration was supported by the administration of oxygen and caffeine. The child responded with noticeable effect after the administration of caffeine.

SUMMARY

A case of acute nicotine poisoning due to a tobacco infusion given per enema is described. The importance of maintaining adequate respiration and restoration of blood pressure is stressed. The nature, action, fate and toxicity of nicotine is presented.

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SPANISH ABSTRACT

Un Caso de Intoxicación Aguda por Nicotina

Los autores relatan el caso de un niño de 2¾ años a quien se administró un enema con una infusión de tabaco como tratamiento antiparasitario casero presentando 15 minutos después, espuma en la boca, vómitos y convulsión generalizada de tipo de grand mal. Después de ésta no pudo caminar, rechinó los dientes y cayó al suelo. A la exploración presentaba: hipotonía y flacidez muscular, palidez, ausencia de reacción a los estímulos, desviación de los ojos hacia arriba, midriasis y parálisis de los músculos intercostales con respiración diafragmática exclusiva, pues la caja torácica no tenía motilidad alguna. Tonos cardiacos algo débiles, pulso filiforme, bradicárdico e irregular, presión arterial no medible e hiporreflexia tendinosa. Se trató con oxígeno, venoclisis de suero glucosado al 2½ y suero de Ringer diluído de medio inicialmente bajo presión y después por goteo, 1 gramo de gluconato de calcio diluído con solución glucosada al 10%, por vía intravenosa y cafeína. A las cinco horas de este tratamiento se apreció franca mejoría y al siguiente día estaba bien. Un nuevo examen a los 7 días demostró estar sano.

Los autores llaman la atención sobre el peligro potencial de este tipo de tratamiento casero para las lombrices y de los insecticidas que contienen nicotina, enfatizando el cuadro agudo de colapso y shock y de parálisis intercostal de instalación rápida como la acción tóxica más peligrosa del veneno, así como el caracter agudo temporal de dicho cuadro y la importancia de la terapéutica de sostén del enfermo en vista de la rápida eliminación del tóxico que favorece grandemente la recuperación del enfermo.

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SIGNIFICANCE OF FEBRILE CONVULSIONS

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CONVULSIVE seizures that attend a febrile illness are significant because of the numbers of children involved. We have no adequate statistics drawn from the general population, but we know that they form a substantial proportion of all young children brought to doctors because of seizures. Of Peterman's 2,500 patients less than 17 years of age, 33.4% had such a history.[1] Among 987 children with convulsive disorders cared for at Johns Hopkins Hospital, 35.4% were classified as febrile. These cases constituted 2.3% of all admissions to the pediatric service, an incidence equal to rheumatic fever and twice that of active tuberculosis. Of 742 epileptic patients seen in their epilepsy clinic, the proportion with febrile seizures was 39% (Bridge[2]). In the present series of 1,136 patients with a history of a convulsive seizure during the first decade, the proportion of febrile patients was 26.2%. (The comparatively low percentage is explained by the relative scarcity of ward cases. In these a seizure is only a detail of the febrile illness, and such children ordinarily would not be seen by the Seizure Service.)

In samplings made at well-baby clinics by Patrick and Levy[3] and in the homes by Thom,[4] 4.2% and 6.7%, respectively, of children had experienced one or more seizures during their first five years. Fever was associated with seizures in 41% of the first series and in 34% of the second. A gross estimate would suggest that something like 2% of children in the community have one or more febrile seizures in their first five years, or perhaps 2.5% at any age. Much scientific interest attends the problems which this form of epilepsy presents.

RELATIONSHIP OF FEVER TO CONVULSIONS

Solution of the mystery of febrile seizures resembles a best-selling "whodunit." Probably most pediatricians would affirm that a seizure which accompanied a fever is an innocent symptom, the counterpart of a chill in an adult, and hence without unpleasant implications for the future and certainly not to be contaminated by the word epilepsy. An aphorism of Hippocrates would give weight to this conclusion. "A convulsion in a fever is good—for that which occasioned the fever is expelled by the convulsion."

Nevertheless, a febrile seizure cannot be so easily dismissed. What are the possible causes of such a devastating symptom which strikes only the occasional child who is ill with an infection? A number of clues present themselves to the Sherlock Holmes type of physician. As with any standard mystery story, guilt may be where at first thought all is innocence. The responsible agent may not be the fever or only the fever. Six other possibilities must first be considered.

1. The fever may be the result, rather than the cause, of the seizure. Violent muscular

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contractions, especially if heat loss is prevented by immersion of the child in a hot bath or by covering with blankets, can increase body temperature by several degrees. However, this contingency rarely confuses because of the rapid drop in temperature which follows cessation of muscular activity. Also, of course, evidence of infection is absent.

2. The seizure may result not from the fever but from the treatment of the infection. Every mother has heard that to flush the toxins of infection she must flood the child's body with fluids. She does not know that excessive hydration may itself precipitate a seizure in a person whose seizure threshold is low. Bridge[2] cites a case. At first signs of a cold, the overanxious mother would put her 9 year old child to bed and force fluids to as much as four quarts a day. After a day or two, he developed headache and later had a generalized convulsive seizure. Fever was never high and seizures did not recur after the forced-fluid regimen was abandoned. Again, sulfadiazine and penicillin placed on the cortex will induce seizures, and large doses administered to the child, perhaps in synergism with the hydration, might conceivably bring on a seizure.

3. The fever may be neither result nor cause of a seizure but may itself be an epileptic seizure. If the perturbation of the electric potentials which underlie epileptic phenomena should be centered in the hypothalamic area for the regulation of heat, then the outward expression of the convulsive would not be alteration of consciousness or muscle movement but a depression or elevation of temperature. Such cases, although rare, are well authenticated, the evidence including abnormal slowing of the brain waves during an attack.

4. Infection and fever are partners in crime, but which is the more responsible? Should we say "infection" rather than "fever" convulsions? A seizure may follow an injection of prophylactic vaccine when the child is afebrile or it may precede an elevation of temperature by a number of hours. Nor does the temperature need to be high. The child may have some "sniffles" with a thermometer registering only tenths of a degree above normal. If the infection itself and the associated circulation of toxins is the important element, certain infections should be more often complicated by seizures than others. A reported rate for scarlet fever is 8%. How does this compare with other exanthemata or with infections like tuberculosis when the toxicity or the fever may be meager? How do infants with tertian malaria react to the periodic hyperthermia? In the 776 cases of Herlitz,[5] 80% involved acute pharyngeal infections. Respiratory and ear infections are also important; 73% in the 455 patients of Pascual and McGovern.[6] Contagious diseases accounted for 11%. Frequency of respiratory tract involvement may be due to the greater prevalence of these infections. Answers to some of the questions raised might be sought by observing the effect of different kinds of infection on the seizures of a given patient, or by studying the convulsive threshold of animals to pentamethylene-tetrazol (metrazol®) convulsions after receiving injections of different bacterial toxins.

5. The seizure may not be primary to the fever but secondary to cerebral pathology. This could result from an invasion of the brain by organisms or toxins, causing encephalitis, meningitis or infection infarcts. Chronic infection plus inanition and severe dehydration can cause venous thrombosis and cerebral destruction. In cases secondary to brain infection, seizures occur late in the illness, perhaps when the temperature is falling, and are most often focal. They are not confined to childhood but sporadic cases may occur at any age. These cases of acquired epilepsy originating in infections that involve the cerebrum need to be segregated from the pure febrile form.

6. A coalition of conditions—toxicity, hyperthermia and various biochemical changes—may act in concert.

Returning to the role of fever alone, Wegman[7] induced seizures in kittens by a rapid rise in body temperature to 4 or 5 degrees above normal through exposure to external heat. High fever without infection may attend a variety of bodily disorders: head injury, cerebral hemorrhage or operation in the region of the third ventricle, lesions of the upper cervical cord, malignant disease, especially hypernephroma and acute leukemia, aseptic thromboses, heat stroke, inanition or dehydration in early infancy, thyroid crisis, serum sickness, drug allergies and the introduction of pyrogens.[8] Convulsive seizures do not commonly attend these conditions although subjects are rarely the very young.

In the absence of experimental evidence to the contrary, we must assume that infection and fever acting together induce so-called febrile seizures. The risk of seizure increases with the temperature. Often times the thermometer seems to act like the safety valve of a boiler—it "blows off" steam (a convulsion) when the pressure (temperature) reaches a certain height, usually 39.4°C. or over. In 75% of Herlitz'[5] cases the temperature was 40.0°C. or over. It was more than 39.4°C. in 40% of white and in 68% of Negro children.[6] The seizure usually appears on the ascending curve of temperature or at its crest. Probably a rapidly rising temperature is more influential than a slow one.

Mechanism of Action

Answer to the convulsive action of infection and fever lies in the area of physiology, but the unknown X must also be kept in mind. A seizure is a rare accompaniment of fever. Even in those subject to this form of seizure, nonfebrile seizures may be sandwiched between the febrile. This X factor—the predisposition or heredity of febrile seizures—is of underlying importance and will be discussed later. The immediate question concerns the mechanism by which infection and fever precipitate seizures in the predisposed. The dehydration and acidosis that accompanies fever and sweating (unless overcompensated by forcing of fluids) should exert an anticonvulsive action. Between the hypothalamus and the adrenal cortex, and involving epinephrine, adrenocorticotrophic hormone (ACTH) and the corticosteroids, chemical factors involve hydration, hypoglycemia, hypocalcemia, hypoxia and alkalosis. Thus, Herlitz[5] observed that seizures occurred at a lower temperature in children with signs of spasmophilia. Also, with spasmophilia, seizures were shorter and, in the same infection, more often multiple and less often one sided. However, he argues in favor of a cerebral anemia as the primary cause. Bridge[2] suggests that because of the proximity of the pituitary gland to the thermal center of the brain, retention of fluid might accompany fever. There should be a serious attempt to coordinate information in the areas of biology and neuro-anatomy.

A generalized alteration in the permeability of cell membranes, including those of the nervous system, seems a plausible explanation of the end effect of infection. Harrell and Aikawa[9] believe this occurs with acute infections. Early in the disease the defect is due to toxic products of the infecting organism and later to an immune reaction. In the latter case, the authors suggest the use of antihistiminics and ACTH or cortisone. The relative absence of convulsive seizures in serum sickness and the fact that "simple" febrile seizures appear early in the infection argue for a direct toxic effect on cell membranes and capillary walls. These mechanisms deserve more adequate study in children.

But why does the body temperature increase in the presence of infection? A plausible theory is that the toxins or products of tissue injury act on the thermo-regulatory centers in the brain. In this event the seizure may not be a consequence of fever, but both fever and seizure a consequence of toxic action on brain cells, a localized action for fever,

generalized for the seizure. Evidence of the effect of body temperature on brain waves is contradictory. Hoagland[10] found increase of frequency. A "speeding up" conceivably could give the final push to the high voltage fast activity which is the "hall-mark" of a seizure. However, in adults fever induced in various ways, with control of the effect of overventilation, resulted in slowing.[11] Brain potentials are slowed even when infection is absent and the fever is a seizure phenomenon. Doubtless, fluctuations in the chemistry of the brain may be influential.

These questions are complicated by another. Why are initial febrile seizures confined to the very young? A greater liability to contract an infection does not explain this. Do the metabolic reactions or susceptibility of the nervous systems of the very young organism differ from those of older organisms? Does the age incidence of febrile seizures parallel, for example, the tendency of the child's brain waves to slow with induced alkalosis? Or does a heightened heredity with its tendency to an early display of symptoms play a part? This suggestion bears on the mystery of the specific action of fever in producing only one of the many varieties of epileptic phenomena, namely, a convulsive seizure.

In addition to the 407 patients in this series who had experienced fever-induced seizures, only 3 or 4 instances were encountered in which the reaction was nonconvulsive. In these exceptional cases there was a sleep-like or coma-like response which might be mistaken for the stupor of fever except for the abrupt onset and termination and the inability of parents to arouse. The tripping mechanism for petit mal is more sensitive than for other seizure types. Persons subject to frequent daily petite absence may have either increase or decrease (but more often an increase) in the number of attacks during an intercurrent infection, but the influence of high fever is less provocative than induced alkalosis. Of course, in early childhood and even without benefit of fever, epilepsy expresses itself most frequently as a convulsion. The developing neuromuscular system seems conditioned to that form of response.

Another curious circumstance is the fact that if a person has a history of both febrile and nonfebrile seizures, those that accompany fever almost invariably come first. Among 313 patients of all ages with a history of seizures both with and without infection and fever, the febrile seizure was clearly primary in 94%. In some of the others, the infection when it came involved the brain. In the discussion that follows, "initial" febrile seizures are spoken of although in 6% of patients they were subsequent to nonfebrile. This experience contrasts with that of Bridge.[2] In his series of 274 cases the nonfebrile "attack" was primary in 43%.

Thus, a febrile seizure is usually the expression of a temporary and reversible change in the biophysics of the brain. However, on occasion it may represent structural and perhaps irreversible changes in nerve cells or conduction pathways, not necessarily attended by neurologic signs. Decision as to whether observed pathology is due to circulating toxins, immune reactions, or to bacterial invasion of the brain usually is not feasible. For these reasons, and because an over-all view was desired, the author has not tried to "weed out" the irreversible cases. In comparing certain clinical correlates of persons with and without a history of febrile seizures, the groups were limited to children whose initial seizure occurred in the first decade of life.

Influence of Age

The preoccupation of febrile convulsive seizure with the immature organism is a puzzling fact. Have convulsive movements been noted in late intrauterine life on the occasion

of a maternal infection? After birth, age of onset may depend somewhat on exposure to infections. In 96 babies with an initial febrile seizure in the first 12 months, only 5% occurred in the first month and 40% in the first 6 months. The first three years are the abundant ones. In the 311 cases of M. Lennox[12] all but 4% occurred in this period. In the larger series of Herlitz[5] the median age was 18 months; that is, half the cases occurred above and half below this age; one-fourth were younger than 11 months, one-fourth older than 29 months, the oldest being 9½ years. (A series based on hospital admissions may be misleading because very young children may be more likely than older to enter a hospital for treatment of an infection.)

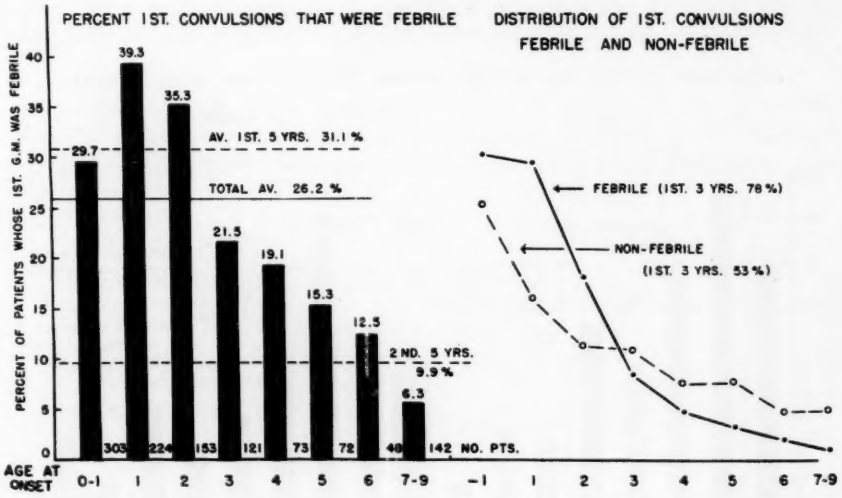

FIG. 1. Right half of figure: Distribution of ages of 298 children at initial fever-induced seizure and of 838 other children at initial nonfebrile seizure. Left half of figure: Proportion of 1,136 children (total of 2 groups) whose initial seizure at given age was fever-induced.

The age distribution of children whose initial seizure occurred in the first decade of life appears in the right-hand portion of figure 1. The graph compares the distribution of 298 children with febrile and 838 with only nonfebrile seizure. The highest proportion of those with febrile seizures, namely, 30.2%, occurred in the first 12 months of life, closely followed by 29.5% for the second year and 18.1% for the third; then a rapid decrease to 1%, the average for the seventh, eighth and ninth years. The largest number of children with only nonfebrile seizures, 25.4%, also occurred in the first year; 16.2% came in the second year and 11.8% in the third. The greatest spread between points of the two curves is for the second year of life. The first three years of the first decade contributed 77.8% of the patients having febrile seizures and 53.4% of those having only nonfebrile. The statistical significance is high ($P = .0005$). This again emphasized the relative predominance of febrile phenomena in the first three years of life.

We computed the percentage of all initial convulsive seizures that were fever-induced at various ages. In the 1,136 patients (298 febrile and 838 only nonfebrile) the initial seizure was fever-induced in 26.2%, as shown in the left hand portion of figure 1. In the

first 12 months 29.7% of first seizures were febrile. The largest proportion occurred in the second year; namely, 39.3%, the year of the greatest spread between the curves in the right hand portion. Following this there was a step-like progression downward to 6.3% in the consolidated last three years. The average for the first five years was 31.1% and for the second five years, 9.9%.

Influence of Sex

Herlitz,[5] Pascual and McGovern,[6] M. Lennox[12] and Peterman[13] found that males formed, respectively, 56, 55, 62 and 56% of the children with febrile seizures. Males are more liable to congenital defects and birth injuries, and male adults have a lower threshold than females to metrazol® seizures. However, to be significant, children with febrile seizures must be compared with those whose attacks are nonfebrile. Of this series, males

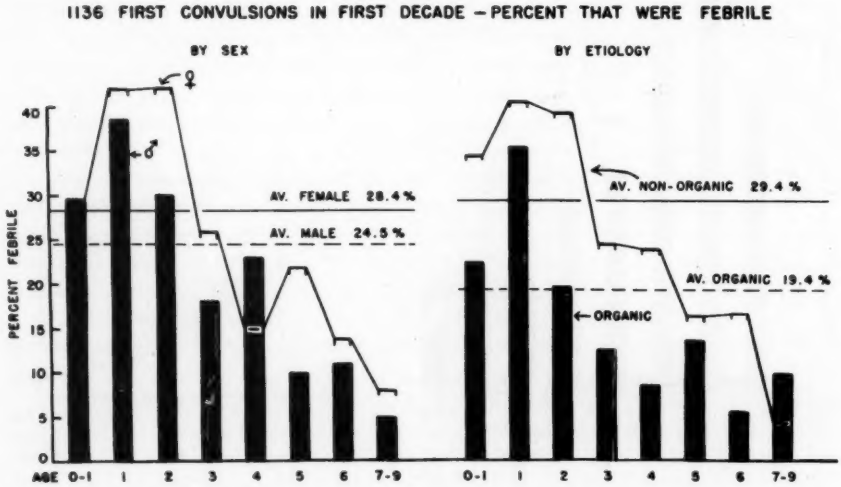

Fig. 2. Proportion of children having first convulsive seizure at given age whose seizure was fever-induced. Left hand of figure compares distribution by age in 493 females (upper graph) with that of 643 males (solid columns). Right half of figure compares etiologic groups: 775 children of non-organic (genetic) group (upper graph) and 361 children of organic (acquired) group (solid columns).

formed 53% of children in the febrile and 57.8% of those in the nonfebrile group. The males seemed slightly less liable than females to experience a fever-induced seizure; 24.5% of 689 males and 28.4% of 447 females had a history of a febrile seizure in their first 10 years. The left hand portion of figure 2 displays the percentage of boys and of girls whose first seizure was febrile. For all years except the fifth year (children aged 4 years), the female ratio exceeded the male. Although the spread is not sufficient to be statistically significant ($P = .3$), a slight preponderance of females might be expected in view of the findings with respect to etiology. Are females either more exposed or more susceptible to febrile infections, particularly respiratory tract infections, than males?

Influence of Etiology

The 1,136 patients were separated into two groups on the basis of whether evidence of

cerebral pathology antedated the initial seizures. The percentage of children in each group whose initial seizures was febrile appears in the right hand portion of figure 2. The genetic or nonorganic group of patients displays a higher proportion of patients with initial febrile seizures than the acquired (organic) group; namely, 29.4% against 19.4%. This difference is highly significant ($P = .001$). Both Herlitz[5] and Bridge[2] emphasize the importance of organic conditions as a background of febrile seizures, but the data here presented belies this conception. Febrile seizures are less common in children with prior brain injury than in those without such etiology. As shown in the chart, the increased incidence is higher in the genetic group for all ages except among children 7 to 9 years of age. This reversal in the older children may be because infection and fever at this age is more likely to be associated with a cerebral involvement which would throw the case into the acquired group.

Influence of Both Sex and Etiology

Is the proportion of females higher in both the genetic and the acquired groups? The height of columns in figure 3 represents the percentage of females in each group. All represent less than 50% because males predominate in the total series. The important point

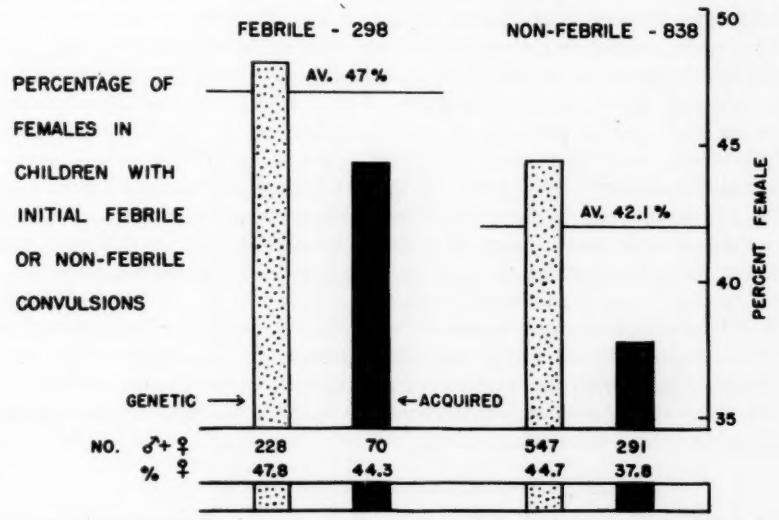

Fig. 3. Percentage of females among children with febrile or only nonfebrile seizures with reference to whether cerebral pathology antedated onset of seizures.

is the relationship between the height of columns in the febrile as contrasted with the nonfebrile groups and between the genetic and acquired subgroups. First, the two columns of the febrile group are higher than those of the nonfebrile. The average for the febrile is 47% and for the nonfebrile, 42.1%. In the febrile group, the proportion of girls is higher in the genetic (47.8%) than in the acquired subgroups (44.3%). Also, in the nonfebrile group the proportion of girls is higher in the genetic (44.7%) than in the acquired subgroup (37.8%). The spread between genetic and acquired is greater in the nonfebrile than in the febrile groups, in keeping with the fact that males are more subject to brain injury, and this factor is more evident when fever is not involved. However, the observed differ-

ences could be due to chance. The "P" values for the groups represented by columns from left to right are: 0.3, 0.8, 0.6 and 0.13.

Office versus Clinic Patients

Economic factors may be important. A relatively high rate might be expected among clinic patients who presumably are exposed to more infectious diseases or else receive less prompt or effective treatment with increased chances of febrile seizures. Also, they would go more quickly to the public clinic than the private patient would be sent to a consultant. Among the clinic patients, febrile seizures formed 28.9% of the initial seizures of the first decade. In the office group the proportion was slightly less, 24.5%. However, the spread between the two groups in the various years was not consistent nor was the total difference significant ($P = .08$).

Repetition of Febrile Convulsions

The 298 children used in the preceding tabulations were augmented from earlier records to a total of 407 cases, this including 15 cases with an initial febrile seizure after the age of 9 years. The individual seizures, when the number was known, were counted. A total of 1,414 seizures were experienced by 390 patients, an average of 4 per person for the genetic and 3 per person for the acquired group. However, 41.8% of the total group had only 1, 13.3% only 2 and 11.3% 3. Thus, two-thirds had no more than 3. Twelve per cent had 4 or 5, 12.3% from 6 to 10, and 9.3% more than 10. Some patients either had many infections and a seizure each time or a series during one or more of their infections. Twenty-four children had a total of from 11 to 19, and 12 had 20 or more febrile seizures.

In the brain-injured group, 58.8% of the 131 patients had but one febrile seizure against 33.2% of the 259 in the uninjured group. In compensation, repeated seizures were more common in the genetic group. Thus, those having 10 or more febrile seizures represented 11.2% of the genetic, and only 5.3% of the acquired group. Fever-induced seizures clearly are linked to genetic (essential) epilepsy.

Several questions remain; namely, what if anything, is the harm of febrile seizures, what are the chances that chronic epilepsy will follow, of what help is the electroencephalograph in distinguishing harmful effects or in foretelling epilepsy, of what importance is heredity in these cases? Finally, are febrile seizures epilepsy, and if so, are they in essence central or peripheral to epilepsy as a whole?

Harmfulness of Febrile Convulsive Seizures

In general, pediatricians have prefaced "convulsions" with soothing adjectives "simple" or "benign" and have shunned the word "epilepsy." However, the benignity of a seizure depends not on its name, but on the severity of the convulsive movements, the degree of apnea and cyanosis, the duration of unconsciousness and whether the seizure is focal or generalized, single or multiple. The initial febrile seizure can be a severe one and can be attended or followed by symptoms of focal brain injury. M. Lennox[12,14] recorded the severity of the seizures in 176 children with a history of febrile seizures only and in 53 children with initial febrile and later nonfebrile seizures. The definition of a severe convulsive seizure was that of Patrick and Levy;[3] namely, if it or the following coma lasted an hour or more and if it started in or involved chiefly one limb or one side of the body. By these criteria severe seizures occurred in 40% of the "benign" group and in 62% of those who later had nonfebrile seizures. She emphasizes also that the existence of high temperature is in itself a complication which would tend to increase rather than decrease

the chances of brain damage. Lesions of the brain may follow fever therapy. A one-sided seizure may be followed by transient hemiparesis, or a generalized seizure during fever may be succeeded by a focal seizure. In children whose seizures lasted more than 30 minutes, hemiparesis occurred in 3.6%.[5] These considerations assume a special weight when, as most often happens, the febrile seizures strike in the first three years of life when nerve cells are peculiarly susceptible to injury. Among 392 patients of the Seizure Unit who sustained brain injury in the first 10 years, the damage was ascribed to febrile seizures in 5.4%.[15]

Subsequent Seizures without Fever

What proportion of children whose initial seizure is fever-induced later on have "spontaneous" seizures? This frequently asked and apparently simple question has received no adequate reply. Young children must be followed into adult life, hence pediatricians are at a disadvantage. Livingston and associates[16] regarded the child with febrile seizures as safe if nonfebrile seizures had not appeared in childhood, obviously too near-sighted a view. In a follow-up of 395 children having infantile seizures (41% febrile), Thom[4] found that 12% had chronic epilepsy. Patrick and Levy[3] reported 4% of nonepileptic patients and 20% of epileptic patients had infantile seizures. In the present author's 407 febrile cases of all ages, 76.9% had subsequent spontaneous seizures. Among 1,900 patients of all ages, 16% had experienced a convulsive seizure at the time of a febrile illness. These backward looks are of little value because the adult portions of these groups were seeking treatment for chronic nonfebrile seizures. Incidence of epilepsy in young adults examined in the draft (0.5%) is only 20% of the incidence of febrile seizures in children suggested in the second paragraph of this study. Addition of persons with "ordinary" epilepsy arising in childhood and later would greatly reduce the percentage. Less than 5% of children whose initial seizure is fever-induced may later have "spontaneous" seizures.

The data reviewed do not permit any precise statement of the chances that the average child with history of febrile seizures will become epileptic. As in all aspects of epilepsy, prognosis is highly individual. If febrile episodes extend for years, especially if the infection is mild, if seizures are severe, focal or long-lasting, or accompanied by deep cyanosis or coma, or if a neurologic deficit results, the outlook is unfavorable. The opposite of these conditions and an increasing length of time since the last attack are favorable. The electroencephalogram may add its evidence, either favorable or unfavorable.

Significance of the Electroencephalogram

Because the EEG has proved of such value in the understanding and diagnosis of epilepsy, observations in relation to febrile seizures are distinctly in order. Such studies present certain difficulties. Records of young children are more difficult to interpret than those of adults, and various significance might be attached to abnormalities when these appear. Several possibilities exist.

First, the abnormality may have existed prior to the first seizure and be the result of brain injury or a transmitted trait. Records made of the parents or of siblings might in the latter case show some degree of abnormality. A survey of infants' records in order to catch the rare one with evidence of preconvulsive dysrhythmia would prove a Herculean task.

Second, abnormalities may be the immediate consequence of a high fever to which the brain had been subjected, and like the slowing which attends hyperpnea, it may be only a transitory and perhaps inconsequential finding.

Third, abnormalities might represent pathology of the brain, a result of the fever, infection or seizure, or of all three. In this event, a focus of abnormality and persistence of the dysrhythmia would be expected.

The pattern of abnormality should provide some clue about these various possibilities. A generalized dart and dome of the 3/second variety suggests a transmitted dysrhythmia, whereas 2/second spike-wave discharges, especially if localized, point to an acquired lesion, although such lesion might antedate the seizure or be a consequence of it, the former being the more probable.

Electroencephalograms were made of all the patients, but since most were subject to spontaneous attacks, results are not applicable. M. Lennox[12] made recordings of 240 children who had a history of febrile seizures, of 373 unscreened, supposedly normal children, and of 295 children who had a history of nonfebrile seizures. The febrile group, compared with the nonfebrile, had more tracings with a background of fast or slow activity, but especially the very slow. It had relatively few with paroxysmal seizure discharges or with a focus of abnormality (cases with infections involving the brain were omitted from the febrile group). The proportion of abnormal records was higher if made within a day or a few days after a febrile seizure (one-half were made within seven days). If sufficient time is allowed to lapse, the EEG may become normal in spite of undoubted persisting brain damage. In a group of 143 "febrile" patients who were followed for a period up to three years, later nonfebrile seizures occurred in 5% if EEG were normal and in from 25 to 50% if records had paroxysmal discharges or were abnormally slow, fast or had focal abnormalities. She emphasizes that febrile seizures are followed by brain damage and chronic epilepsy only rarely, but nevertheless such a rare case warns against a "hands off," "wait and see" policy with respect to recurrent fever-induced seizures.

Assignment of responsibility can be puzzling, as in the case of a 4 yr. old child seen in the Seizure Clinic. A maternal cousin had seizures as an infant. Patient spent 5 postnatal days in an oxygen tent, which suggests that her birth had been complicated. On her 2nd birthday, she had a prolonged generalized febrile convulsive seizure, a rash appearing only on 2nd day. Second seizure was without fever. It, like the first, lasted an hour or more. She had been sitting in bed and for half an hour could not speak and drooled saliva; then began a seizure involving L face, arm and leg. Jerking continued on this side for half an hour until intravenous medication was given. Subsequent EEG displayed several bursts of high-voltage slow waves, more pronounced in R parietal lead, and also a run of sharp spikes lasting 2 or 3 sec. in this lead. Daily use of phenobarbital 32 mg. was recommended. Eight months later there had been no recurrence of seizure, but the EEG (Fig. 4)

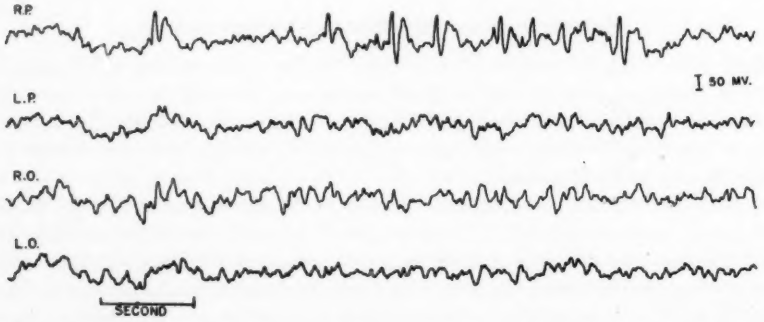

FIG. 4. Four leads of 8-lead electroencephalogram of T. Swe. R.P. and L.P. indicate leads from R and L parietal areas; R.O. and L.O. from R and L occipital. Signal at right measures 50 mv., line at bottom 1 sec. time; monopolar, recording scalp to interconnected ears, was used.

showed even more clearly a spike and spike-wave focus in R parietal area, with occasional slowing in all leads. Consequently, continued medication was advised. The EEG focus may have existed since birth but because first seizure was generalized, probably both the spike-wave focus and its underlying pathology resulted from the initial prolonged seizure, or the infection which caused both fever and seizure.

Period of Time Between

Concern is felt as to when, if ever, spontaneous convulsive seizures will follow those that are fever-induced. The interval between the two types is longer if the patients questioned are adult. In the series of M. Lennox[14] the interval varied from a few months to 25 years, but the majority were within one year. In the present author's series the distribution of time intervals of 313 cases was as follows:

Nonfebrile Appeared	No. Patients	Per cent
Prior to febrile	20	6.4
At about same time	21	6.7
1 to 12 mo. later	147	46.9
1 to 4 yr. later	54	17.3
5 to 9 yr. later	47	15.1
10 to 14 yr. later	14	4.5
15 to 35 yr. later	10	3.1
Total	313	100.

Nearly 23% of children with febrile seizures had five or more seizure-free years (7.6% had 10 or more years) before the onset of spontaneous seizures. The interval was from 22 to 27 years in six cases and 35 years in one. Obviously, a time limit cannot be set beyond which there can be no recurrence. The cause of recurrence is usually uncertain. Of 50 cases having onset of secondary nonfebrile seizures after the age of 9 years, 64% began in the first half of the second decade, 18% in the second half, 14% in the third decade and 4% in the fourth.

No matter what the age of the epileptic patient, or what his form of seizure, a febrile illness, like any disturbing event, may "trigger" one of his many seizures. However, simple fever-inspired seizures will definitely cease with childhood, and subsequent "spontaneous" seizures will appear in only a few.

Types of Nonfebrile Seizures

What form do subsequent spontaneous seizures assume? That point was determined from 272 patients. The distribution of types and combination of types was compared with the distribution in 1,900 office patients of all ages. About 16% of this latter group had a history of febrile seizures, a fact that would tend somewhat to increase the representation of seizures in the control group.

	Febrile Group Per cent	Mixed Group Per cent	Value of P.
Grand mal only	52.0	46.6	.2
Grand and petit mal	6.3	20.4	.0005*
Grand mal and psychomotor	7.9	13.0	.008*
Total with grand mal	66.2	80.0	
Petit mal only	11.5	9.8	.4
Psychomotor only	17.1	5.9	.0005*
Other forms or all three	4.3	4.3	.2
Total	100.0	100.0	

* Results highly significant.

The tabulation discloses that grand mal (alone or combined) was more frequent in the mixed than in the febrile group by 13.8 percentage points. The significant increase for the febrile group is the relatively large number of patients with only psychomotor seizures as the subsequent seizure pattern, 17.1% for the febrile against 5.9% for the mixed group, a nearly three-fold increase. (In the febrile group, the proportions were 15% for the genetic subgroup and 23.5% for the acquired.) This finding suggests that the febrile seizures of early childhood may in certain cases cause injury to the temporal lobe (with its vulnerable vascular arrangement) with, in later life, inception of psychomotor seizures. Supportive evidence from a different source has been presented in a study of psychomotor epilepsy.[17]

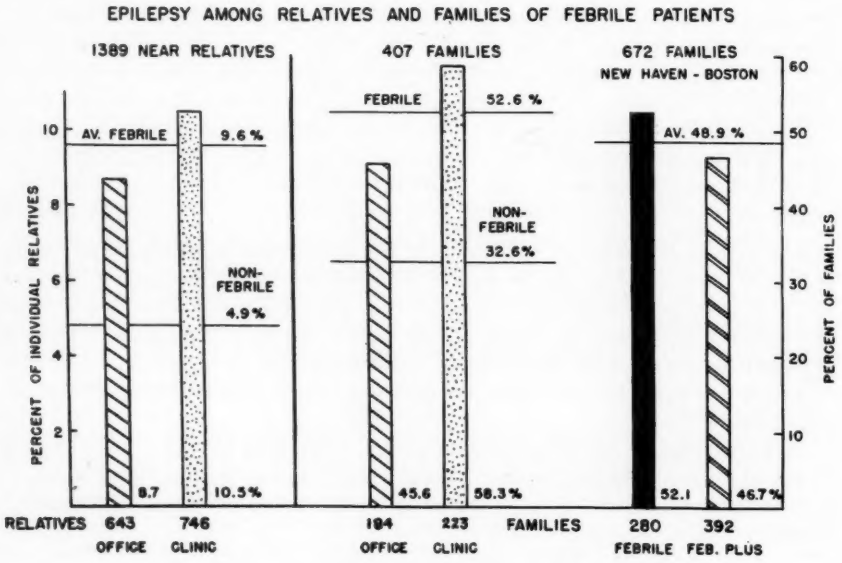

FIG. 5. Epilepsy among relatives and families of febrile patients.

SIGNIFICANCE OF HEREDITY

All epilepsies are either genetic or acquired (or a resultant of both). The genetic form represents epilepsy at its purest, uncomplicated and unadulterated by the many acquired conditions which can cause seizures. Evidence for a constitutional-transmitted origin of seizures means a pure culture of epilepsy and a relatively good prognosis. Twin data would be most informative, but in such a small group chance plays a large role because of a varying exposure or susceptibility to infection. In the author's series of 138 epileptic twins, 15 had a history of febrile seizures. Both co-twins were affected in 6 out of 9 monozygotic and in 2 out of 6 dizygotic pairs.

Livingston et al.,[16] M. Lennox,[14] Peterman[18] and F. A. and E. L. Gibbs[18] reported that persons with a history of febrile seizures also have an unusually prominent family history of epileptic seizures. The author combined the data of M. Lennox from New Haven with this present series from Boston. In the combined series slightly more families were affected if seizures were febrile only (52.1%) than if febrile were later followed by nonfebrile

seizures (46.7%). Of the total 672 families represented, 329 or 48.9% were affected. (Two right hand columns of figure 5.)

Comparison was next made between the 407 patients with a history of febrile seizures and 539 other patients without such history, but whose nonfebrile seizures began in their first five years. Of the 407 febrile children, 214 or 52.6% had some relative with epilepsy. Of the 539 children of the nonfebrile group, 176 or 32.6% had an epileptic relative, a difference of 20 percentage points. In figure 4 the two horizontal lines in the central panel represent these values. The two columns in this central panel illustrate that the genetic influence in the febrile group is somewhat greater among clinic than among office patients (a family history in 58.3% of clinic patients, dotted column, against 45.6% of office patients, hatched column).

For confirmatory and more accurate information the author computed the incidence of epilepsy among the near relatives of the "febrile" epileptic patient, that is, incidence among individuals rather than among families. The 407 children of the febrile group had a total of 1,389 parents and siblings. Of these, 134, or 9.6%, had had one or more seizures. The larger group of 539 children without history of febrile seizures had 2,207 relatives of whom 124 or 4.9% were epileptic. This is only about one-half of the incidence (9.6%) for relatives of children with a febrile convulsive history. (Horizontal lines of the left hand panel of figure 5.) The two columns of this left hand panel compare clinic patients (10.5%) with office patients (8.7%). The difference is not in itself significant, but the direction of spread (45.6% for the office and 58.3% for clinic families) is the same as for the incidence among families.

In summary, the incidence of epilepsy among the 1,389 relatives of children with febrile seizures for various subgroups of patients was as follows:

	Brain Uninjured Per Cent	Injured Per Cent	Total Per Cent
Office patients	10.6	5.8	8.7
Clinic patients	13.2	4.9	10.6
Male patients	10.8	6.2	9.0
Female patients	13.3	4.0	10.6
All patients	12.1	5.3	9.6

This tabulation agrees with data from much larger groups of patients collected without regard to febrile seizures in demonstrating the greater incidence of epilepsy among relatives of patients without antecedent brain injury. Increases for clinic and female patients are relatively unimportant. Important is the high incidence (9.6%) of epilepsy among the near relatives of those who had experienced an early febrile seizure. The incidence among 3,148 relatives of children with a seizure of any sort in the first year of life was 5.3% (6.4% for the uninjured and 2.9% for the injured group).[19] Corresponding percentages for relatives of the febrile group should be lower because most of these fevered patients were older than one year, but actually rates were nearly twice as high, 12.1 and 5.3%, respectively (bottom line of tabulation).

Thus, the greater genetic quality of patients with a history of febrile seizures is well established. Additional questions then arise. Is there transmission of a tendency not simply to seizures but to fever-induced seizures? And again, since the febrile attacks of patients usually number only one or two, are the seizures of affected relatives, whether febrile or not, also few in number? In other words, eliminating the factor of some acquired brain injury, is the quality of mildness or transience in seizures a transmitted quality? Answer

to these important questions is especially difficult because details of a first babyhood seizure of a relative may be lacking. The parent of a febrile convulsant child often volunteers the information that he, or some of his siblings, experienced febrile seizures without subsequent seizure phenomena. This, for the parent, is a reassuring thought. In the series of M. Lennox[12] 199 patients with only febrile seizures had 90 relatives with seizures. In 76 (84.4%) of these, seizures were rare.

Family histories such as the following support the thought that response to infection (or fever) with a seizure (without resulting chronic epilepsy) is an hereditary quality. In the following case, impetus to the seizure may have been reinforced by a predisposition gained from the mother, as evidenced by her EEG.

A girl, 4½ yr. of age, beginning at 2½ yr. had 7 convulsions in sleep, each when she had some throat infection and a temperature of 38.8°C. or more. EEG displayed a discharge lasting 2 sec. of fast spikes and waves in occipital leads. Placed on 3,5,5-trimethyloxazolidine-2, 4-dione (tridione®) for treatment of the ailing EEG, a year later this was free of seizure discharge and the child had had neither infection nor seizure. Similar cases dangle on the family tree—a total, including patient, of 7 persons; father, father's mother and 2 paternal cousins and patient's 2 siblings, each has had febrile seizures and a sister, aged 15 yr., has had migraine since 4 yr. of age. Brain waves of father and this sister were normal. Mother is ignorant of her family history, but she herself gives a story of vague periods of "dizziness." Her EEG was abnormal because of ½ sec. bursts of stubby spikes in all leads and infrequent low voltage spike-wave formations in L anterior temporal lead.

The case that follows illustrates both a familial tendency toward fever-induced seizures and the pathophysiology which may accompany a febrile seizure and perhaps contribute to subsequent spontaneous ones.

A Cuban boy 3 yr. of age, during an infection of tonsils and fever of 40.0°C. had a R-sided seizure lasting 40 min., followed in an hour by a second one. After each of these R arm and leg were helpless for several hours, although affected limbs participated in second convulsion. Subsequently, he has had a dozen nonfebrile generalized seizures and many astatic seizures. Neurologic examination and an EEG of him and his sister were normal, but following a generalized seizure, his record displayed generalized seizure discharges. Four paternal cousins had infantile seizures, 3 fever-induced, 1 not; 1 of 2 sisters had had 2 febrile seizures, mother and paternal grandmother and aunt are subject to migraine.

The focal pathophysiology responsible for focal seizure and consequent palsy presumably was not based on anatomic lesion because the palsy did not prevent participation in subsequent seizure and was transient. However, a focal abnormality probably activated the subsequent chronic epilepsy.

After careful analysis of his data, Herlitz[5] concluded that in addition to a recessive, a dominant factor may play a role in febrile seizure. If the view is accepted that evidence of hereditary transmission is the hall-mark of uncomplicated, idiopathic, genetic epilepsy, then a febrile seizure is epilepsy. But more than that, it is an unusually pure culture of epilepsy.

This conclusion has a corollary. Fever-activated epilepsy is short-lived. The majority of children with such seizures have only 1 or 2. Therefore, the more pure (or essential) the epilepsy, the better the outlook for spontaneous recovery. The more complicated the epilepsy by manifest causes, the worse the prognosis. Stating this in reverse, the more chronic the epilepsy, the more impure or atypical it is. The diagnosis of a disease does not depend on a persistence of its symptoms. To be a "real" epileptic patient, the person need not suffer through the years. Seizures uncomplicated by acquired pathology of the brain (either gross, microscopic or perhaps only biochemical) tend to be short-lived, perhaps even self-limited—limited by the stabilizing influence of age. Such a conception provides a broad silver lining for the dark cloud of current thoughts about epilepsy and

adds force to the appellation "Epilepsy, the Hopeful Disorder." This conception, generally accepted, should counteract some of the prevailing snobbish attitudes toward this illness. On this point, a sentence from the study of M. Lennox[12] may be repeated: "To the objection 'but we can't call febrile convulsions epilepsy, for if we do, then some of our best people have epilepsy', we can only assent that some of our best people do, indeed, have epilepsy."

Summary

In a child, a convulsive seizure in association with fever may mean 1 of 6 things.

1. The fever may be a consequence of a spontaneous seizure, the results of an excess of muscular energy and heat.

2. The seizure may be the result of excess hydration or of antibiotics given to combat an infection.

3. The fever may be a seizure phenomenon, the result of a paroxysmal seizure discharge in the region of the hypothalamus.

4. The seizure may be due not to the fever but to bacterial toxins.

5. It may be the secondary result of cerebral pathology induced by an invasion of the brain by the infectious organisms.

6. The seizure may be due to no one of these, but be the direct response of the young child's organism to high fever in association with some infection. In addition, the seizure may not be the consequence of fever, but both fever and seizure a consequence of toxic action on brain cells.

Curious features as yet not satisfactorily explained are.

1. Fever-induced seizures belong predominantly to the very young.

2. Almost invariably the febrile seizure, if there is such, is the child's initial seizure.

3. Response to fever is almost invariably a convulsion rather than some other manifestations of epilepsy.

A study was made of 1,136 persons whose first convulsive seizure occurred in the first decade of life, 298 having had fever-induced seizures (usually with subsequent nonfebrile), 838 having had none. The two groups were compared with respect to age at the first seizure, the presence of antecedent brain pathology, the sex of patients and whether seen in clinic or office. Extreme youth and absence of pathology were most often associated with febrile seizures. Among a total of 407 fever-activated cases, 76.9% subsequently experienced nonfebrile seizures. In 22% an interval of five years or longer separated the last febrile seizure from the first nonfebrile one.

With respect to the type of subsequent seizures, an undue proportion of patients had only psychomotor seizures, suggesting that febrile seizures may sometimes be attended by temporal lobe lesions.

Febrile seizures are usually innocuous, but if prolonged, focal or attended by much cyanosis or protracted coma, they may cause brain damage. Of 392 patients who sustained brain injury in the first 10 years of life, febrile seizures were blamed for the injury and the continuing epilepsy in 5.4%.

Most notable of these findings, however, is the confirmation of what others have reported, that the genetic influence in children having fever-induced seizures is unduly high. In the author's group, this influence, as measured by the incidence of epilepsy among near relatives, is approximately double the genetic influence in young children having only nonfebrile seizures.

If we accept the view that evidence of hereditary transmission is the hall-mark of

essential epilepsy, then a febrile seizure is epilepsy; but more than that, it is an unusually pure culture of epilepsy. This conclusion has a corollary. Fever-activated epilepsy is short lived. The majority of children with a history of fever-induced seizures have had only one or two. Therefore, the more pure or essential the epilepsy, the better the outlook for spontaneous recovery. Seizures uncomplicated by some acquired pathology of the brain tend to be short lived, perhaps even self-limited—limited by the stabilizing influence of age.

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Spanish Abstract

La Significación de las Convulsiones Febriles

En un niño, una convulsión asociada con fiebre puede significar una de las seis posibilidades siguientes:

1. La fiebre puede ser la consecuencia de una convulsión espontánea, resultado de un exceso de energía muscular y de calor.

2. La convulsión puede ser el resultado de exceso de hidratación o de antibióticos dados para combatir una infección.

3. La fiebre puede ser un fenómeno no convulsivo resultado de una descarga convulsiva paroxística en la región del hipotálamo.

4. La convulsión puede ser debida no a la fiebre sino a las toxinas bacterianas.

5. Puede ser el resultado secundario de un padecimiento cerebral inducido por una invasión del cerebro por organismos infecciosos.

6. La convulsión puede no ser debida a alguna de estas causas, sino la respuesta directa del organismo juvenil del niño a la fiebre alta en asociación con alguna infección. Además, la convulsión puede no ser la consecuencia de la fiebre sino que ambas, fiebre y convulsión, la consecuencia de una acción tóxica sobre las células cerebrales.

Las características que aún no se explican satisfactoriamente son:

1. Las convulsiones inducidas por la fiebre pertenecen predominantemente a los niños muy pequeños.

2. Casi invariablemente la convulsión febril, si existe, es la convulsión inicial del niño.

3. La respuesta a la fiebre es casi invariablemente una convulsión mas bien que alguna otra manifestación de epilepsia.

Se hizo un estudio en 1.136 personas cuya primera convulsión ocurrió en la primera década de la vida; 298 de ellas habían tenido convulsiones inducidas por fiebre (generalmente con convulsiones subsiguientes no febriles) y 838 no tuvieron ninguna. Se compararon los dos grupos con respecto a la edad en que tuvieron la primera convulsión, la presencia de antecedente cerebral patológico, sexo de los pacientes y si se habían visto en la clínica o en el consultorio. La niñez extrema y la ausencia de patología estuvieron mas frecuentemente asociadas con convulsiones febriles. Entre un total de 407 casos activados por fiebre, 76.9 porciento experimentaron subsecuentemente convulsiones no febriles. En el 22 porciento la última convulsión febril estuvo separada de la primera convulsión no febril por un intervalo de cinco años o mas.

Con respecto al tipo de las convulsiones subsecuentes, una proporción exagerada de pacientes solo tuvo convulsiones psicomotoras, sugiriendo que las convulsiones febriles puedan algunas veces ser acompañadas de lesiones del lóbulo temporal.

Las convulsiones febriles generalmente son innocuas, pero pueden causar una lesión cerebral si son prolongadas, focales, acompañadas de mucha cianosis o coma persistente.

De 402 enfermos que presentaron lesión cerebral en los primeros diez años de la vida, en el 5.2 por ciento se culpó a las convulsiones febriles y a la epilepsia que continuó, como causantes de la lesión.

Sin embargo, lo más notable de estos hallazgos es la confirmación de que la influencia genética en los niños que tienen convulsiones inducidas por fiebre es exageradamente alta, lo cual ha sido ya reportado por otros. En nuestro grupo, esta influencia, medida por la incidencia de la epilepsia entre los familiares cercanos, es aproximadamente el doble de la influencia genética en niños pequeños que tienen solamente convulsiones no febriles.

Si aceptamos el punto de vista de que lo que define la epilepsia esencial es la evidencia de su transmisión hereditaria, entonces una convulsión febril es epilepsia, aún mas que eso, es un extraordinario cultivo puro de epilepsia. Esta conclusión tiene un corolario. La epilepsia activada por la fiebre es de corta vida pues la mayoría de los niños con historia de convulsiones inducidas por fiebre han tenido solamente una o dos. Por lo tanto, entre más pura o esencial es la epilepsia, son mayores las posibilidades de recuperación espontánea. Las convulsiones no complicadas por patología cerebral adquirida tienden a ser de corta duración, aún quizas limitadas por sí mismas, limitadas por la influencia estabilizante de la edad.

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EOSINOPHILIA-HEPATOMEGALY SYNDROME OF INFANTS AND YOUNG CHILDREN

Report of a Case Due to Invasion of Liver by Nematode Larvae

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CASES with chronic eosinophilia of ill-defined eitology, such as tropical eosinophilia (Weingarten's disease, Frimodt-Möller's syndrome), familial eosinophilia, Löffler's syndrome, eosinophilic pseudoleukemia and various others, have been studied for many years. A newly recognized syndrome with the prominent feature of chronic eosinophilia has become apparent in infants and young children. During the past five years, five different authors have reported a total of 14 infants and young children with this syndrome of chronic eosinophilia, hepatomegaly, and liver biopsy findings of eosinophilic infiltrative and granulomatous lesions.

The common features of the syndrome are a benign asymptomatic course unless associated with pulmonary lesions, an age incidence at onset of from 15 to 38 months, chronic persistent hyperleukocytosis with moderate to severe eosinophilia, hyperglobulinemia, hepatomegaly and eosinophilic infiltrative and granulomatous lesions in the liver. A number of patients, in addition, have pulmonary infiltrations as demonstrated in chest roentgenograms. They have the symptoms of mild to moderate pneumonitis, recurrent in some cases. Between episodes, they are asymptomatic and well.

The syndrome has all the aspects of an antigen-hyperergic disease. The antigen has proved to be nematode-larvae invasions of the liver in four cases, including the present one. It is probable that larvae migrations in the liver and other viscera are the cause in all cases.

The purpose of the present communication is to draw attention to the existence of this newly recognized syndrome, to present an analysis of the findings in 15 reported cases, and to report an additional case in which the etiology was proved to be liver invasion by a nematode larva.

CASE REPORT

A 21 mo. old white female infant was referred because of moderate eosinophilia and hepatomegaly. These findings were discovered 2 mo. previously during a routine examination.

Infant was born at Fort Belvoir, Va., as the result of 3rd pregnancy of a normal mother. Pregnancy was uneventful and delivery was normal. Infant developed normally, although she was said to have been a poor feeder and a "colicy" baby. She had repeated episodes of rhinorrhea and "wheezy" chest colds with cough after age of 4 mo. At 10 mo. of age, she had a mild attack of acute laryngotracheobronchitis. Eosinophilia was not present at that time, liver was not enlarged, and chest RGs were negative for pulmonary infiltrations.

Except for periodic "wheezy" colds and cough, infant had been well, and growth and development had been normal for her age.

Family had never owned dogs or cats. A history of pica and dirt-eating was not obtained. Blood counts obtained on both parents showed no eosinophilia.

Physical examination revealed a well nourished and developed infant, who appeared to be in

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excellent health. Abdomen was prominent, and liver was palpable 3 cm. below R costal margin. Spleen was not outlined, and lymphadenopathy was not present. Lungs were clear and heart was normal.

The admission blood count showed RBC 4.40 million/mm.^{3}, Hgb. 14 gm./100 cc., WBC 17.2 thousand/mm.^{3} and differential count was neutrophils 27, lymphocytes 35, mononuclears 5, and eosinophils 33%.

Extensive studies were carried out to determine cause of the eosinophilia and hepatomegaly. Many hematologic examinations have shown hyperleukocytosis of 13.5 to 26.5 thousand/mm.^{3}, and eosinophilia of from 26 to 36%, which has persisted. Anemia has not been present, and abnormal or young cells have not been seen in peripheral blood. Bleeding and clotting times have been normal. Bone marrow study reflected eosinophilia of the peripheral blood in that there was eosinophilic hyperplasia. There was no evidence of a leukemoid condition. Urine has been normal. Numerous stool examinations, including flotation and concentration methods, have all been negative for ova and parasites. Strongyloides parasites were not present in duodenal secretions. Complement fixation tests of blood were negative for Echinococcosis, amebiasis and trichinosis. Total blood proteins were 7.5 gm./100 cc., albumin 4.1 gm./100 cc., globulin 3.4 gm./100 cc. and A/G ratio of 1.2. Quantitative Van den Bergh determinations have been within normal limits. Liver function tests, including thymol turbidity, zinc sulfate turbidity, and cephalin flocculation, were normal. Several chest RGs were negative. A complete allergy work-up failed to reveal any remarkable findings. Skin sensitization tests showed only minor reactions to house dust and monilia albicans. There were no reactions to pollens. Tuberculin skin test and serology were negative.

It was thought that the case was probably one of the syndrome under discussion. Accordingly, exploratory laparotomy was performed, and a liver biopsy obtained. At operation, liver was seen to be enlarged and studded with a moderate number of grey-white plaques, measuring 0.5 to 4 mm. in size. Selected liver tissue for biopsy was excised and sent to laboratory for study.

Pathologic Findings: Examination of pilot sections, stained with hematoxylin and eosin, showed areas of normal parenchymal cells, but throughout were heavy infiltrations by inflammatory cells. Predominantly, these were eosinophiles, although plasma cells and small round cells were also present. The infiltration varied from circumscribed lesions in portal triad areas without involvement

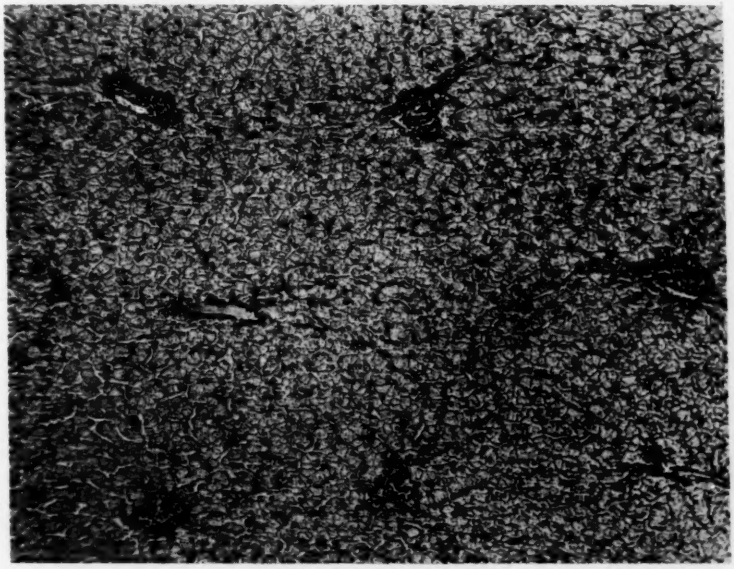

FIG. 1. Liver. Uninvolved central vein, numerous portal triads showing cellular infiltrate. H & E × 120.

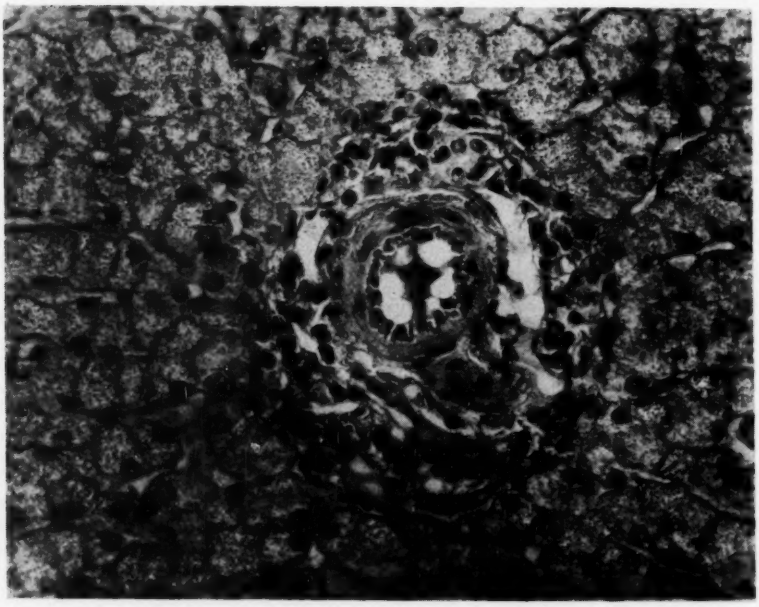

FIG. 2. Liver. Portal triad showing infiltrate but no vasculitis. H & E × 475.

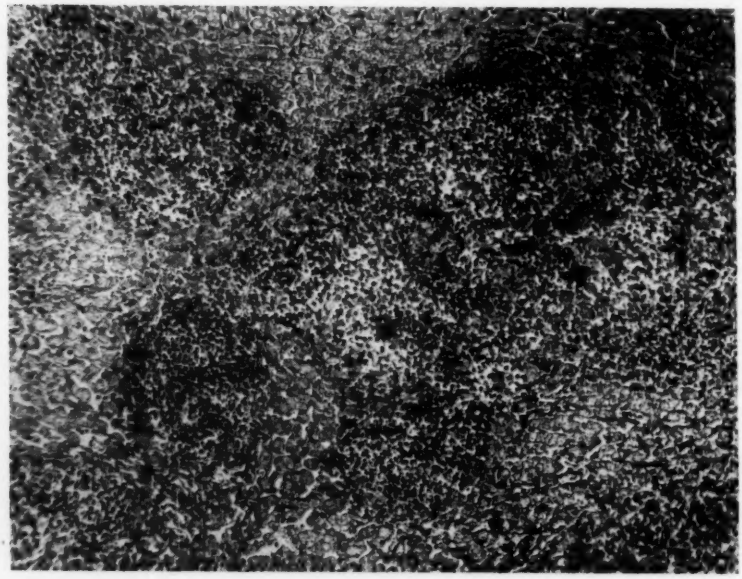

FIG. 3. Confluent area of exudate and liver-cell loss. H & E × 120.

of lobule centers (Figs. 1 and 2) to more extensive confluent ones showing bile capillary and fibroblastic proliferation. The latter lesions frequently merged into large confluent areas of tissue loss (Fig. 3). These large areas of involvement were irregular in outline, poorly circumscribed, and involved indiscriminately all zones of the lobule and adjacent lobules. In these lesions, rare epithelioid cells and foreign body type giant cells were visualized, but peripheral zones of lymphocytes and fibrous tissue of granulomatous lesions were absent.

Initially, bacteria, parasites or foreign body material were not discernible in the sections. Skip serial sections were then prepared. Each section was cut at 6μ thickness. Of each 11 sections, 10 were discarded and the 11th one stained and examined. Each of the latter sections thus represented a depth of tissue amounting to 66μ. The skip serial sections revealed a parasitic larva continuing

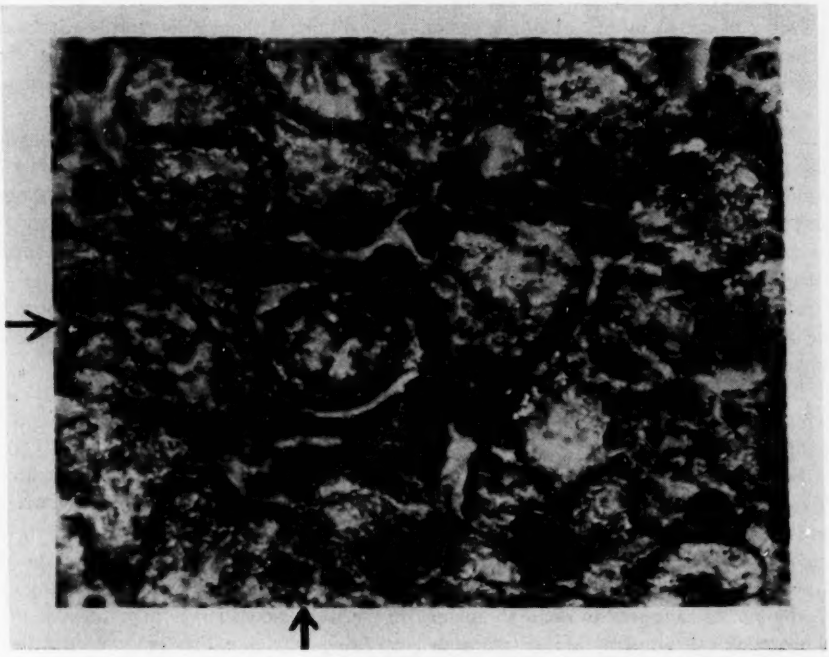

FIG. 4. Parasite, midportion. Divided lumen, lateral spines. H & E × 1000.

through 5 of the sections. The larva thus traversed tissue of a depth of 330μ. Since remaining sections failed to reveal the head and tail portions, length of the larva was little more than 330μ. Diameter of the larva varied from 17.4 to 20.9μ. Cross section of larva (Fig. 4) showed a circular structure with a fairly well developed outer shell, a suggestion of a divided lumen and bilateral spines. Small basophilic nuclei were seen between the lumen and the outer shell. In one distal section the divided lumen and lateral spines were no longer present, but more numerous basophilic nuclei were seen. It was not possible to identify the exact type of the larva but the diameter and estimated length agree with that of the dog ascarid, Toxocara canis, as described by Beaver et al.[1] in their reported case. Diameters of the larva of parasites commonly infesting man and which might lodge in the liver (Ascaris lumbricoides, Strongyloides stercoralis, Trichinella spiralis and Ancylostome) are smaller than that of the larva in this case. Hence, although an exact identification could not be made, it is suggested that the larva was that of Toxocara canis.

Patient, now 33 mo. of age, has been observed for a period of 1 yr. The hyperleukocytosis, eosinophilia and hepatomegaly have persisted, and have been known to exist for at least 14 mo. Last blood count was WBC 14.8 thousand/mm.^{3} with 33% eosinophilia. She has been asymptomatic

and well during this period and has continued to grow and develop at a normal rate for her age. No specific treatment has been administered.

Discussion

History of Syndrome: The realization that these cases make up a syndrome and represent a true clinical entity has occurred only recently. Prior to 1947, a number of cases which we can now probably recognize as belonging to this syndrome was reported under various names. Stewart[2] reported two such cases in 1933; Valledor,[3] four in 1939; Bass,[4] three in 1941; and Selander,[5] one in 1945. There are probably others.

Perlingiero and György[6] reported the observations and clinical course of a case in the presence of ascaris infestation of the gastrointestinal tract. Although no nematode larva or other parasites or organisms were found in the lesions of the liver, they mentioned the possibility that the hepatic lesions may have been on the basis of an allergic response to ascaris toxin.

Zuelzer and Apt[7] reported the largest single group of eight cases. No definite etiologic agent could be proved in any of their cases. The one and only death among cases with this syndrome, to the authors' knowledge, occurred in their group. It was the autopsy findings in this case, their first, that stimulated their interest and led to their search and discovery of seven additional cases. These authors should have the credit for being the first to recognize that these cases comprise a syndrome as distinct clinical entities.

Mercer et al.[8] reported a case with typical findings of the syndrome. For the first time, a definite etiologic agent was found in the pathologic liver lesions; namely, a nematode larva, which they identified as Ascaris lumbricoides.

Behrer[9] described another case with all the cardinal features of the syndrome and in which, for the second time, the larva of Ascaris lumbricoides was found in the liver as the exciting etiologic agent.

Beaver[1] and his group reported three cases. In one of these, they discovered the larva of Toxocara canis, a dog ascarid. Because of the identical findings in both the clinical courses and the pathologic hepatic lesions in their other two cases and in those cases previously reported by others, they postulated that the syndrome is probably caused by nematode larvae migrations through the liver and other viscera in every case. The larvae migrations in the viscera suggested to them an analogy to the well known larvae migrations of the skin, called creeping eruption or cutaneous larva migrans. Hence, they proposed that this syndrome be designated as "visceral larva migrans."

Pathogenesis and Etiology: There is good evidence, as agreed by all who have studied these cases, that the syndrome results from localized antigen-hyperergic tissue reactions with the predominant lesions occurring in the liver. These lesions are histologically similar to those of other hyperergic conditions, such as Löffler's syndrome,[10] rheumatic tissue changes[11] and the vascular changes in periarteritis nodosa.[11]

The causative antigen or antigens have been identified in only four cases. The proved antigens in these cases were hepatic invasions by the larvae of Ascaris lumbricoides in two,[8,9] by larvae of Toxocara canis in one[1] and by an unidentified larva, but probably Toxocara canis, in the present case. The antigens in 11 other cases were not found, but various possible ones, such as pollens, bacterial infections and drugs were postulated.

Although proof is lacking in every case, the authors are of the opinion that migrations in the liver and other viscera by nematode larvae are probably the exciting antigenic agents in every case. These larvae, in liver sections, can easily be missed, as they are found only

TABLE 1

ANALYSIS OF 15 REPORTED CASES WITH SYNDROME

	Age Onset (mo.)	Known Duration (mo.)	Av. Leukocytosis 1000/m³	Av. % Eosinophilia	Hepatomegaly	Hyperglobulinemia	Liver Biopsy-Eosinophilic Lesions	Liver Function Tests	Etiology Found	Allergic Background	Course	Pulm. Infilt.
Case 1[6]	24	15	55.0	45	+	+	+	+	A. lumbric. in stool	Yes	Fever Pneumonitis	+
Case 2[7]	36	1	?	?	+	?	+	?	None	?	Died Pneumonia Convulsions	+
Case 3[7]	25	30	24.8	40	+	+	+	+−	None	No	Benign	−
Case 4[7]	18	6	43.0	36	+	+	+	+−	None	No	Fever Pneumonitis	+
Case 5[7]	38	6	11.9	20	−	?	No biopsy	?	None	No	Benign	−
Case 6[7]	24	4	98.0	87	+	+	+	+−	None	Yes	Benign	−
Case 7[7]	24	3	50.1	52	+	+	No biopsy	−	None	Family	Benign	−
Case 8[7]	36	36	35.8	40	−	+	No biopsy	?	None	No	Pneumonitis Lead poisoning	+
Case 9[7]	36	18	8.8	21	+	+	No biopsy	+−	None	No	Benign	−
Case 10[8]	24	2	38.0	62	+	+	+	+	Larvae A. Lumbricoides in liver	Family	Fever Pneumonitis	+
Case 11[9]	15	2	55.9	50	+	+	+	+	Larvae A. Lumbricoides in liver	No	Benign	−
Case 12[1]	16	14	45.0	70	+	−	+	−	None	No	Benign	−
Case 13[1]	26	6	21.7	62	+	?	+	−	None	No	Pneumonitis	+
Case 14[1]	30	21	50.0	30	+	?	+	?	Larvae Toxocara canis in liver	?	Benign	−
Case 15 (present case)	19	14	20.0	30	+	+	+	−	Larvae probably Toxocara canis in liver	Yes	Benign	−

TABLE 2

FREQUENCY OF SYMPTOMS IN 15 CASES WITH SYNDROME

	No. Cases Found	
Hyperleukocytosis	15	
Eosinophila	15	
Onset under age 3 yr.	14	(1 case 38 mo.)
Hepatomegaly	13	
Eosinophilic granulomata of liver biopsy	11	(all cases that had laparotomy and biopsy)
Hyperglobulinemia	10	(present in all cases, except 1, where determination made)
Benign course, asymptomatic	9	
Mild pneumonitis with RG infiltration	6	
Allergic background to usual allergens	5	
Larvae in liver	4	(Ascaris lumb.—2; Toxocara canis—1; Probable Toxocara canis—1
Positive liver function tests	3	
Positive stools for ova and parasites	2	(Ascaris lumbricoides)
Convulsions	2	(1 died)
Death	1	

after prolonged and detailed searches for them with use of special technics. In addition to the incrimination of larvae in four cases, other factors in support of visceral larvae invasions as the cause are: 1. The well known fact nematode parasites are powerful antigenic agents. 2. The fact that the sites of the lesions, in the liver in all cases, and evidence of additional lesions in the lungs in others, coincide with the paths of migratory nematode larvae in man (through the intestine, portal circulation, liver, heart and lungs). 3. The finding of keratin material, which could be the moult of larvae, in the microscopic liver sections of a number of cases where actual larvae could not be found. (The keratin from ascaris larvae has been shown to be a potent eosinophilatactic agent.[12]) 4. Evidence that ascaris larvae can produce lesions in the lungs comparable to those in the livers of these cases.[13] 5. The fact that all the cases have occurred in infants and children under 3 years of age, a period when there is greater exposure to infestations through dirt-eating and increased hand to mouth activity.

Analysis of 15 Cases with Syndrome: Data pertaining to 15 reported cases are shown in tables 1 and 2. The hematologic picture, other than the hyperleukocytosis and eosinophilia, is not remarkable. Anemia may or may not be present. Blood clotting mechanism is normal. The ESR may or may not be increased. Bone marrow studies reveal only eosinophilic hyperplasia.

The reason for the age distribution in infancy and young childhood, assuming all of them to be caused by visceral invasions of larvae, might be explainable by the increased exposure to infestations through dirt-eating during this age period. Also, the relative sizes of the larvae as they pass through the liver and the liver capillary beds may be important. Larvae increase in size as they migrate through the liver and heart to the lungs by moulting a number of times. They are much smaller when in the liver than when they are in the lungs. This fact together with the relative sizes of the liver capillary beds of infants and young children compared to adults may well explain the limitation of this syndrome to the

former. The larger hepatic capillary beds of adults allow the smaller larvae, before they have increased in size, to pass through the liver to the lungs (Löffler's syndrome?); whereas, the smaller capillary beds in infants arrest the larvae in the liver to cause the hepatic syndrome. Perhaps differences in immunologic responses characteristic of this age group may be involved.

The size of the liver varies, but usually it is mildly or moderately enlarged, nontender and smooth. Associated enlargement of the spleen has been noted in a number of the cases.

Mild to moderate increase in the globulin fraction of the plasma proteins is almost a constant finding. The total proteins may be normal or increased. The albumin/globulin ratio is usually reversed, due to an increase in globulin and not to a decrease in albumin.

Exploratory laparotomy and liver biopsy have been performed in 11 of the 15 cases. In every case explored and biopsied, lesions of an eosinophilic infiltrative and granulomatous nature, identical in every case, have been found in the liver. At operation, the liver is found to be enlarged and the surface to be studded with a number of irregular-shaped white or grey plaques, varying in size from a few to 8 mm. Microscopic sections of liver biopsies show focal necrosis, granulomas with epithelioid cells, histiocytes and giant cells. and widespread eosinophilic infiltrations. Reports on the pathologic material of the 15 cases indicate variations from case to case, suggestive of differences in duration and severity of the process. Early lesions of eosinophilic infiltrations alone, focal necrosis and granulomas may be seen, or older healing lesions with fibrosis, encapsulation and even calcification may be observed.

Liver function is usually not impaired. The liver function was impaired, and then only to a mild degree, in only three cases.

Jaundice has not been noted. Van den Bergh determinations have all been within normal limits. Ascites, hypoproteinemia and hypoalbuminemia have not occurred.

Allergic backgrounds were noted in the past histories of five of the patients (asthma, hay fever, "wheezy colds" or family history of allergy).

Course and Prognosis

The course is a benign one and the prognosis is good. The majority of the cases (9) have been completely asymptomatic. In the remaining six, symptomatology was incidental to a type of pneumonitis, consisting of recurrent attacks of fever, cough and parenchymal infiltrations in chest roentgenograms. However, these patients were never acutely ill, and were asymptomatic between the respiratory disease attacks and later when the attacks subsided.

The disease appears to be a self-limited one, but of long duration. In only one case did the eosinophilia completely disappear, and this after a period of three years.[7] The eosinophilia, hepatomegaly and other findings have persisted in all the other 14 patients during observation periods of from 1 to 30 months. In spite of this, all of them have been well with normal growth and development.

There was only one death in this group. This case, reported by Zuelzer,[7] was that of a 3 year old child, who died within a few hours after admission to the hospital with wheezy respirations, high fever and convulsions. Eosinophilic hyperplasia of the bone marrow was present, and the typical eosinophilic granulomas were found in the liver. The anatomic cause of death at autopsy could not be determined by them.

Treatment

Since past experience indicates the syndrome is a benign one with good prognosis, specific treatment does not appear to be necessary. Treatment with various vermicidal agents in a number of cases, and with cortisone in one case has been reported by other authors. The courses of the disease in these cases were not appreciably altered by the medications.

Summary

Attention is directed to the existence of a recently recognized syndrome in infants and young children with the prominent features of chronic eosinophilia, hepatomegaly, liver biopsy findings of eosinophilic infiltrative and granulomatous lesions, a benign course, and occasionally symptoms and signs of transient pneumonitis.

An analysis of 15 reported cases with the syndrome is presented, including the report of a case due to an unidentified nematode larva, but probably Toxocara canis, invading the liver.

Signs and symptoms, pathology, pathogenesis, etiology, course and prognosis, and treatment are discussed.

Evidence is preponderantly in favor of the etiology in all cases being nematode larvae invasions of the liver and other viscera.

These cases cause conjecture as to whether other diseases of chronic eosinophilia, such as Löffler's syndrome, tropical eosinophilia, familial eosinophilia and pseudoleukemic eosinophilia, may not also be due to visceral nematode larvae migrations. Further investigation is warranted in these diseases.

Acknowledgment

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SPANISH ABSTRACT

El Síndrome Eosinofilia Hepatomegalia de los Lactantes y Niños Menores; Reporte de un Caso Debido a la Invasón del Hígado por Larva de Nemátodo

El objeto de esta comunicación es llamar la atención acera de la existencia de este nuevo síndrome, hacer un análisis de los signos y síntomas y relatar un caso más cuya etiología fué la invasión por la larva de un nemátodo.

Por muchos años han sido estudiados casos con eosinofilia crónica cuya etiología ha sido vaga que se les ha denominado eosinofilia tropical, eosinofilia familiar, síndrome de Löeffler, pseudoleucemia eosinofílica, etc., y en los últimos cinco años diferentes autores han reportado un nuevo síndrome en niños pequeños que actualmente hacen un total de catorce casos.

Las características comunes de este síndrome son: curso benigno asintomático a menos que esté asociado con lesiones pulmonares, principio más frecuente entre los 15 y 38 meses de edad, hiperleucocitosis crónica persistente con moderada a severa eosinofilia, hiperglobulinemia, hepatomegalia con infiltrado eosinofílico y lesiones granulomatosas en el hígado reportada en aquellos casos en que se hizo laparatomía y biopsia hepática. Además, cierto número de enfermos presentan infiltraciones pulmonares demostradas radiológicamente y las manifiestan clínicamente por neumonitis ligera o moderada, a veces recurrente, estando asintomáticos y bien entre dichos episodios.

El síndrome tiene todos los aspectos de una enfermedad antígeno-hiperérgica y en cuatro pacientes, incluyendo el de los autores, se ha probado que el antígeno es la larva de un nemátodo que invade el hígado, siendo muy probable que la emigración de las larvas al hígado y a otras vísceras sea la causa en todos los casos.

El enfermo a que se refiere el artículo es el de una niña de raza blanca, de 33 meses de edad, que tenía leucocitosis intensa con eosinofilia, de caracter crónico y persistente y hepatomegalia desde la edad de 19 meses. Tenía como antecedentes el haber sido un lactante con cólicos frecuentes y episodios repetidos de catarros bronquiales con estertores silbantes. Estudios extensos revelaron hiperglobulinemia y debido a la hepatomegalia se le hizo laparotomía exploradora encontrándose un hígado sembrado de placas blanco-grisáseas, de ½ to 4 mm. de tamaño, infiltración eosinofílica y lesiones granulomatosas en las secciones microscópicas de la biopsia hepática. Estas ultimas lesiones eran idénticas a aquellas que han sido atribuídas a una reacción antígeno-hiperérgica y a las que han sido reportadas previamente en lactantes y niños con el mismo cuadro clínico del caso en cuestión. Los exámenes repetidos de las evacuaciones y secreciones duodenales fueron negativos para huevecillos y parásitos. Cortes en serie del tejido hepático obtenido por biopsia revelaron una larva con longitud mayor de 330 micrones y diámetro de 20.9 micrones y aunque no pudo hacerse su identificación exacta, su tamaño está más de acuerdo con el de la toxocara canis que con el de cualquier otro parásito.

Los autores hacen conjeturas acerca de si otros padecimientos como la eosinofilia crónica, la eosinofilia familiar, eosinofilia tropical, pseudoleucemia eosinofílica, etc., podrían ser causados también por migraciones viscerales de larvas de nemátodos.

Letterman Army Hospital

TREATMENT OF MENINGITIS WITH CHLOROMYCETIN PALMITATE®

Results of Therapy in Twenty-three Cases

By GARRETT E. DEANE, M.D., J. EARLE FURMAN, M.D., ALICE R. BENTZ, B.S., AND THEODORE E. WOODWARD, M.D.
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SEVERAL groups of investigators[1-4] have reported the beneficial effects of chloramphenicol in meningitis caused by H. influenzae and N. intracellularis. More than 100 cases of influenzal meningitis have been successfully treated with chloramphenicol administered orally or intramuscularly as hydrochloride. The results obtained by this simplified regimen are comparable to earlier therapeutic regimens for H. influenzae meningitis.[5] In 30 patients with meningococcal meningitis the results have been gratifying.[3] The authors have avoided multiple antibiotic therapy and have relied upon a single drug in treating meningeal infections.

Chloramphenicol is effective in the treatment of experimentally-produced gram-positive infections although experience in the management of human infections is not extensive. Pneumococcal lobar pneumonia in infant and adult patients has yielded to its action.[6,7]

Twenty-three pediatric patients, ill with pyogenic meningitis, have been treated with chloramphenicol during the past year. The results of therapy in 12 patients with H. influenzal meningitis, 8 with meningococcal meningitis and 3 with pneumococcal meningitis are reported.

CHLOROMYCETIN PALMITATE®

The need for a palatable liquid preparation of chloramphenicol is apparent in pediatric patients particularly because of the difficulty in administering capsules. Several esters of chloramphenicol, including chloromycetin palmitate®, have been prepared. Chloromycetin palmitate® is one of the hydroxyl groups of the propane-diol chain which has been replaced with an ester group. The esterfied derivative contains approximately 57% chloramphenicol and, as such, is practically devoid of antibiotic effect. Therapeutic activity depends upon the rate of hydrolysis of the ester to the free alcohol form which is mediated through the action of bile and intestinal lipases. The chemically active compound is not formed until it reaches the small intestine and under these conditions the undesirable irritative gastritis is avoided. It has been determined that lipase activity even in ill children remains of a sufficient degree to hydrolyze chloromycetin palmitate®. Indeed, preliminary trials[8] in patients with steatorrhea and pancreatic fibrosis indicate that lipase activity of the succus entericus occurs in sufficient degree to split chloromycetin palmitate® as measured by the blood levels of free chloramphenicol. Preliminary therapeutic trials with the palmitate derivative have shown it to be orally effective.[9]

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Method of Study

Selection of Cases: The patients presented were diagnosed as having influenzal, meningococcal and pneumococcal meningitis. They were admitted to University and Mercy Hospitals from April 1951 to March 1952. Signs and symptoms typical of meningitis were present in each case. Patients' ages varied from 1 to 48 mo., average 16.8 mo. All were acutely ill. Of the 23 patients, 9 had received treatment with other antibiotics prior to admission. Nevertheless, admission spinal fluid cultures were positive in each of these cases. Of this group of 9 patients 4, with H. influenzae meningitis, had been treated with penicillin and sulfadiazine and one with penicillin alone. Three patients with meningococcal meningitis had been treated with penicillin and one with aureomycin.

Method of Administration and Dosage: On detection of purulent spinal fluid following initial lumbar puncture, specific therapy was immediately begun. Chloramphenicol hydrochloride was given

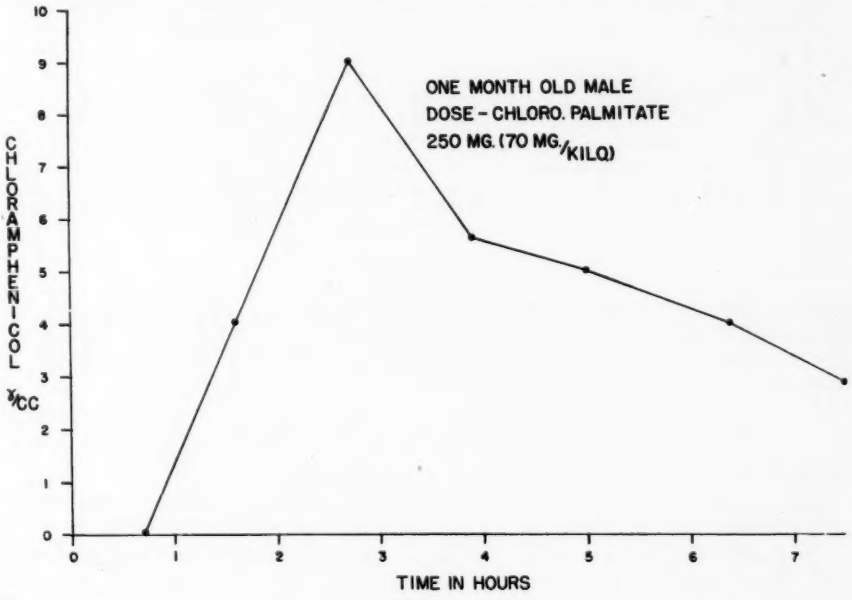

Chart 1

intravenously in dosage of 50 mg./kg. body weight to those patients who were vomiting or comatose. As long as the patient's clinical condition necessitated intravenous therapy, he received intravenous drug in divided 6 hourly doses calculated on basis of 50 mg./kg./day. Dose of intravenous chloramphenicol varied from 0.25 gm. to 3.2 gm. with an average of 1.3 gm. Following intravenous medication, chloromycetin palmitate® was given in dosage of 150 mg./kg./day in 19 cases and 100 mg./kg./day in 4 cases. Eleven patients received chloromycetin palmitate® alone.

Prior observations with the above dosage conducted in normal patients had revealed levels of chloramphenicol of 10 to 30 γ/cc. in blood and 5 to 15 γ/cc. in spinal fluid. Concentration of chloramphenicol in blood of a normal patient who received a single dose of chloromycetin palmitate® is shown in chart 1. Highest concentration was obtained in 3 hr. after initial administration.

Intravenous administration was particularly helpful in those patients who were critically ill and vomiting. On utilizing the intravenous route prompt high concentration of antibiotic appeared in blood and spinal fluid.

The antibiotic was administered until patient was afebrile for approximately 5 to 7 days, provided cultures of spinal fluid were sterile and pleocytosis was noticeably improved. As shown in table 1 the average duration of treatment was 11.9 days.

TABLE 1

Patient (mo.)	Age (mo.)	Sex	Wt. (kg.)	Treatment		Duration of Fever (hr.)	Residuals	Spinal Fluid				Blood Culture	
				Day Started	Duration (days)			Initial WBC/cmm.	Direct Initial Smear	Culture 1st Hr. Found Neg.		Initial Smear	1st Hr. Found Neg.
1	12	M	10.5	3	8	48	No	300	Neg.			Neg.	—
2	23	F	11.0	5	13	24	No	13,984	Pos.			Neg.	—
3	8	F	5.5	2	11.0	24	No	2,700	Neg.			Pos.	24
4	9	F	7	2	14	168	No	4,000	Pos.			Pos.	72
5	9	M	7.7	8	6	168	Died	17,286	Pos.		Pos. to death	—	—
6	16	M	?	1	8.5	48	No	3,200	Pos.		36	Pos.	24
7	1	F	4.5	2	6.75	32	No	920	Pos.				
8	7	F	6.4	2	10.75	72	Bilat. subdural effusion	680	Neg.		24	Neg.	—
9	7	F	7	2	16	72	No	605	Pos.		24	Pos.	24
10	15	F	9.1	4	11.0	14	No	1,440	Neg.		36	Pos.	24
11	24	M	12.3	7	5	3.5	No	1,885	Neg.		—	Neg.	—
12	3	M	7	0.5	17	120	Right subdural effusion	2,160	Pos.		48	Pos.	24
13	36	M	12.5	2	9.5	24	No	10,500	Pos.		24	Neg.	—
14	48	M	15	4	6	24	No	894	Pos.		—	Neg.	—
15	46	F	15	2	14	120	No	9,000	Pos.		24	Pos.	—
16	36	F	14	2	8	24	No	10,200					
17	12	M	10	3	8	24	No	2,435	Pos.		24	Neg.	—
18	48	M	20	3	9.0	24	No	15,350	Pos.		24	Neg.	—
19	3	F	5	7	29.0	24	Bilat. subdural effusion	9,500	Pos.		24	Neg.	—
20	6	M	8	5	8	24	Strabismus	3,500	Pos.	(29)	48	Neg.	—
21	9	F	9	3	7	48	No	1,000	Pos.	(18)	48	—	—
22	7	F	6.8	2	12.5	48	No	424	Pos.	(12)	36	Neg.	—
23	2	M	4.0	7	28	144	Bilat. subdural effusion	293	Pos.	(29)	12	Neg.	—

H. Influenzae
N. Intracellularis
D. pneumoniae

In addition to specific measures, intravenous infusions of glucose and saline were given to maintain electrolytic balance. Transfusions of blood were administered when indicated. A few of the very severely ill patients received cortisone acetate as a supplemental aid to therapy and will be reported later.

Laboratory Methods of Diagnosis: Additional laboratory tests were performed in order to confirm the diagnosis of meningitis. Spinal fluid was centrifuged and cultured and smear of sediment was stained by Gram's method. Etiologic diagnosis was usually made after examination of smear. Spinal fluid leukocyte, differential white blood cell counts, concentrations of protein, glucose and chloride were determined initially and on subsequent specimens obtained later in course of illness.

Urinalyses, hemoglobin, white blood cell counts and cultures of blood and nasopharynx were performed prior to initiation of specific therapy and daily during active stages of infection.

Upon isolation of etiologic organism from spinal fluid, sensitivity tests of bacteria to antibiotic were determined by the disc method.[10] On several occasions, tube-dilution technic was employed. Although the disc technic is not as reliable as tube-dilution method, evidence of bacterial resistance to the antibiotic was not detected.

In order to define the comparative therapeutic effectiveness of chloromycetin palmitate®, bioassays of the antibiotic in blood serum and spinal fluid were performed frequently during the course of therapy. In most instances, therapeutic concentrations of chloramphenicol were detected in blood and spinal fluid using the turbidimetric method.[11] Blood levels ranged from 0 to 23 γ/cc. Concentration of antibiotic in spinal fluid was usually one-third of level obtained in blood. However, in several instances, significant antibiotic concentration was not detected in blood or spinal fluid even though the clinical response was satisfactory.

Results of Therapy

Laboratory Results: Twelve patients (table 1) were shown to have H. influenzae meningitis, type B. In six of these patients, the initial blood cultures were positive and in each patient the spinal fluid was initially positive. Following the institution of specific therapy in 11 of these cases, spinal fluid were found to be sterile on an average of 33.6 hours. From this point onward, H. influenzae were not isolated from the blood or spinal fluid. In the twelfth case, the spinal fluid cultures were positive until death.

Eight patients had meningitis caused by N. intracellularis (table 1). This organism was isolated from the spinal fluid in each case and in one, an initial bacteremia was demonstrated. Spinal fluids became sterile in each patient in approximately 27.4 hours after instituting therapy and in none were subsequent cultures of the blood or spinal fluid positive.

In three patients, meningitis resulted from invasion by types 29, 18 and 12 D. pneumoniae (table 1). The spinal fluid in these patients became negative after three days of treatment. Bacteremia was not demonstrated in these cases.

In this entire series, the spinal fluid glucose ranged from 0 to 58 mg./100 cc. fluid, average 32.2 mg./100 cc. In two patients with influenzal meningitis, the concentration was less than 10 mg./100 cc. Within 24 hours after the institution of specific therapy and after the intravenous fluids, the level of glucose had approached relatively normal limits.

A polymorphonuclear pleocytosis was uniformly observed which ranged from 293 to 17,286 white blood cells/cmm. In 14 patients, an increase of the spinal fluid white cell count occurred up to 48 hours after the institution of specific therapy. This leukocytic response has been noted before[2] and is regarded as beneficial. However, in Case 8 (table 1) the spinal fluid leukocytic count was 140,000/cmm. on the second day of disease and undoubtedly indicated extensive meningeal exudate. In the patients with a transient increase in white blood cells, cultures of the spinal fluid were uniformly sterile after 24 hours of specific therapy. Pleocytosis gradually diminished as convalescence progressed in the patients with H. influenzae, meningococcal and pneumococcal meningitis.

Clinical results: There was complete recovery in 22 of the 23 patients ill with pyogenic meningitis. One patient (Case 5) succumbed to an overwhelming H. influenzae meningitis. In the patients successfully treated, the temperatures returned to normal levels within 2.1 days after beginning specific therapy regardless of the severity of illness, age of the patient or the type of organism isolated from the blood and spinal fluid. In four instances, a spontaneous elevation of temperature occurred during convalescence which subsided uneventfully although the nature of this elevation was not completely determined.

The clinical response to therapy was actually more striking than the favorable influence upon the febrile course. In each of the 22 recovered cases, there was uniform improvement of the clinical condition within 24 to 36 hours after institution of specific therapy. Within this period, those patients initially semicomatose or delirious became mentally clear and were able to take nourishment by mouth. Although irritability was noticeable in patients previously comatose, the improvement was unmistakably apparent. In six patients in whom an accurate history was feasible, headache had markedly abated within the first 24 hours after instituting therapy.

All patients were able to take the chloromycetin palmitate® orally after the first 24 hours in spite of the original severity of their illness. In addition, these patients were able to take nourishment by mouth. After 48 hours of therapy, the patients had gained in strength and vigor; they manifested interest in their surroundings and became more cooperative. Except for the slight elevations of temperature previously mentioned, convalescence in the 22 patients was uncomplicated with the exceptions discussed below.

Complications: One patient (Case 14) developed a reaction presumably caused by chloramphenicol. After an apparent satisfactory recovery (tenth day of treatment) from influenzal meningitis, this four year old boy developed a scarletinaform rash and a fever of 39.4°C. The pharynx was moderately injected and cultures of the blood and spinal fluid were negative. Thirty-six hours after discontinuing chloromycetin palmitate®, the temperature had reached normal levels, the rash had fully abated and the patient's course was thereafter uneventful.

Four patients in this series developed subdural effusions which were detected after the first week of hospitalization. Drainage of the subdural spaces was accomplished by repeated subdural taps. Bilateral trephining was performed in each case, and any subdural membranes removed utilizing the method described by Ingraham and Matson.[12]

Case 5 developed internal hydrocephalus which ultimately led to death. This patient's illness was first detected on the eighth day of disease and specific therapy was then instituted after considerable exudate had accumulated in the subarachnoid space. In spite of energetic therapy which included the intraventricular installation of streptokinase, death occurred after seven days of therapy.

Illustrative Case Reports

Pneumococcal Meninigitis Treated with Chloramphenicol: Patient 22, S. W., a 7 mo. old Negro female, was hospitalized because of fever, listlessness and vomiting. Two weeks previously, she experienced a nonspecific upper respiratory infection. Three days prior to admission she became listless and on the following day developed fever, nausea and vomiting.

In the hospital, the patient was lethargic and irritable. Temperature was 40.5°C. She was moderately dehydrated but no skin petechiae were noted. Anterior fontanelle was bulging. Nuchal rigidity was present and Kernig's and Brudzinski's signs were positive. Pharynx and ear drums were moderately injected. Pupils were equal and reacted to light.

Spinal fluid was cloudy with 424 WBC/cmm. of which 97% were polymorphonuclear. Organisms were observed in spinal fluid smear and culture was subsequently positive for D. pneumoniae, type 12.

An initial dose of chloramphenicol 800 mg. was given intravenously followed by chloromycetin palmitate® 250 mg. at 6 hr. intervals. This was continued for 12½ days. There was definite improvement in 24 hr. and return of temperature to normal levels in 48 hr. Subsequent hospital course was uneventful. Subdural taps were negative on 10th day of illness and patient was discharged on 13th hospital day without evidence of residuals. A follow-up examination 2 mo. following discharge revealed a normal 9 mo. old female. Growth, development, neurologic examination and EEG were within normal limits. Pertinent findings are given in figure 1.

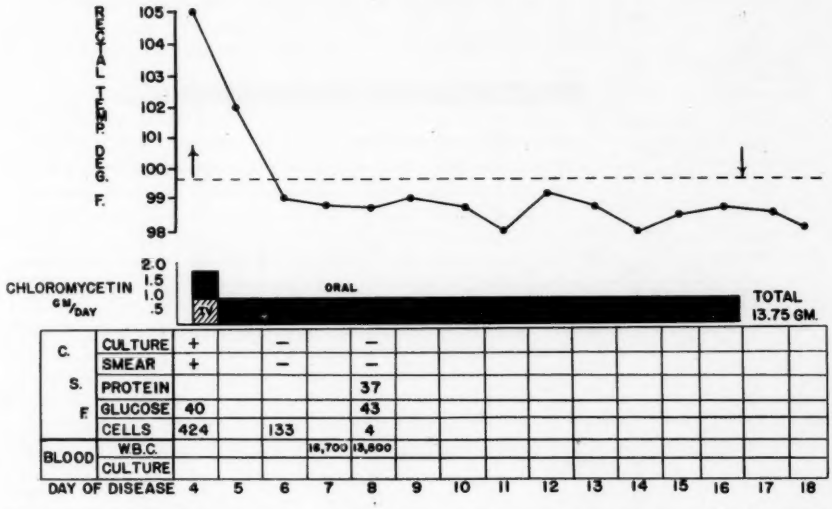

FIG. 1. Case 22. Clinical course of 7 mo. old female with pneumococcal type 12 meningitis treated successfully with intravenous and oral chloromycetin palmitate®.

H. Influenzal Meningitis Treated with Chloramphenicol: Patient 7, A. C., a 7 wk. old Negro female, became ill with fever 2 days prior to admission. The fever abated for one day but recurred and was associated with vomiting. On admission the temperature was 39.7°C. The patient was irritable but no nuchal rigidity was elicited. The anterior fontanelle was tense and bulging and there was generalized spasticity of all the extremities. The deep tendon reflexes were equal and active. The pharynx and ear drums were not injected.

Lumbar puncture revealed cloudy spinal fluid which contained 920 leukocytes of which 98% were polymorphonuclear. The spinal fluid glucose level was 24 mg./100 cc. A few pleomorphic gram-negative rods were seen on the smear and the culture was subsequently positive for H. influenzae, type B.

The patient received chloromycetin palmitate® 500 mg. every 6 hr. The medication was well tolerated and in 48 hr. the temperature was normal. On the fourth day subdural taps were negative. The patient continued to improve and was discharged on the eleventh hospital day, apparently cured. In 2 mo., growth, development and neurologic examination were normal. EEG tracings revealed a normal pattern (Fig. 2).

Fatal Case of H. Influenzal Meningitis Treated with Chloramphenicol: Patient 5, J. B., 9 mo. old Negro male, was admitted on the eighth day of a febrile disease. He received at home 300,000 units of penicillin, sulfadiazine and alcohol sponging for pyrexia. The temperature abated on this regime until the day prior to admission. Muscle twitching, lethargy and anorexia were present during the 8 day period.

When hospitalized, the temperature was 39.5°C. The child was deeply lethargic, lying in extreme opisthotonos. All extremities were rigid. Marked nuchal rigidity was present. A positive Brudzinski and Kernig sign was obtained.

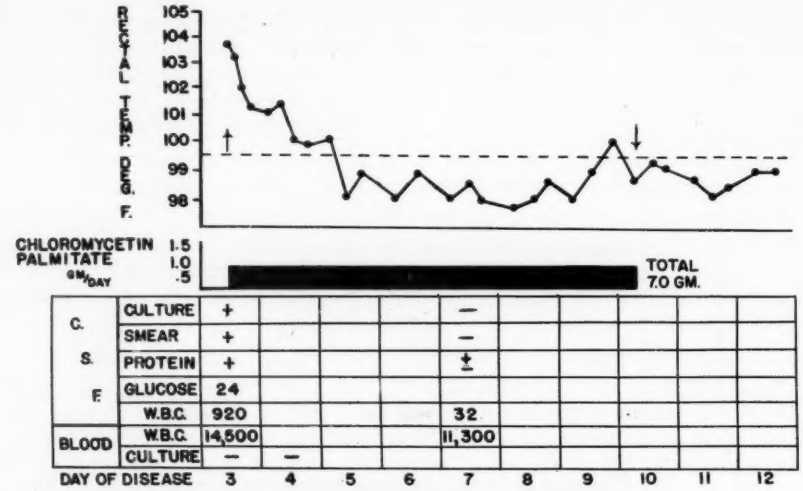

FIG. 2. Case 7. Clinical course of 7 wk. old female patient with influenzal type B meningitis treated with oral chloromycetin palmitate®.

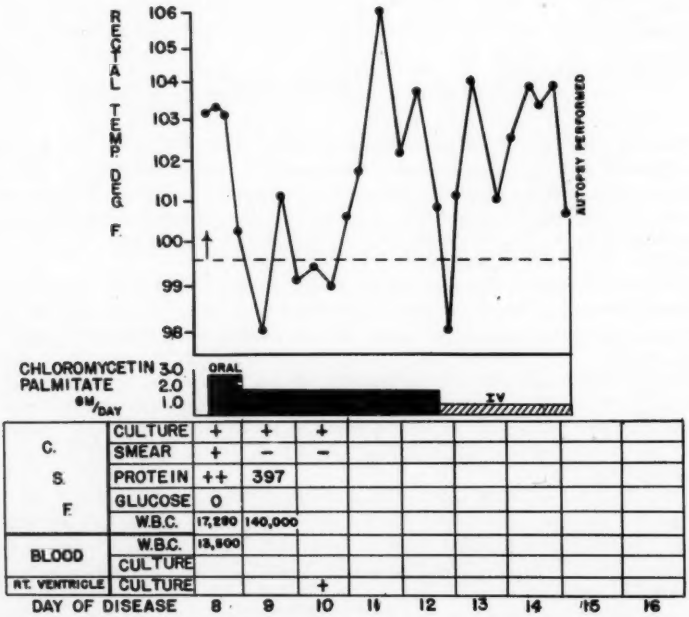

FIG. 3. Case 5. Fatal case of influenzal type B meningitis in 9 mo. old male treated on eighth day of disease with intravenous and oral chloromycetin palmitate®.

The spinal fluid was under an initial pressure of 330 mm. H_2O with WBC 17.3 thousand/cmm. The smear revealed numerous pleomorphic gram-negative rods, subsequently identified as type B, H. influenzae. The patient received chloromycetin palmitate® 600 mg. immediately followed by 300 mg. every 4 hr. by stomach tube.

On the second treatment day the pleocytosis was 140,000/cmm. and the fluid was so viscid that it was obtained through #18 spinal needle with great difficulty. Numerous shreds of thick exudate were removed in this manner. This extensive exudative reaction was surmised to be indicative of a block in the subarachnoid space. Following the removal of 20 cc. of greenish, yellow, cloudy fluid, 60,000 units of streptodornase were instilled into the right ventricular space. Aspiration from the right ventricle 5 hr. later produced 20 cc. of cloudy fluid which was under markedly increased pressure. An additional 60,000 units of streptodornase was instilled. A #15 polyethylene tube was placed into the right ventricle through which intermittent drainage was performed at hourly intervals.

In spite of the above attempts at enzymatic debridement, the patient continued to drain markedly purulent cerebrospinal fluid. Cultures of the lumbar and ventricular fluid continued positive for H. influenzae, type B, in spite of chloramphenicol levels ranging from 5.5 to 12.5 γ/cc. The child died on the seventh hospital day and at postmortem examination, a thick purulent membrane covered the entire brain surface. Pertinent findings are shown in figure 3.

Meningococcal Meningitis Treated with Chloromycetin Palmitate®: Case 14, a 4 yr. old white male, was hospitalized because of pyrexia and a diffuse purpuric rash. The 1st 4 days of illness were characterized by signs of an upper respiratory infection and fever. Repository type penicillin 300,000 u. failed to improve the clinical condition.

When first examined in the hospital, the boy was toxic, acutely ill, irritable, but cooperative. The temperature was 38.8°C. and the blood pressure 130/96 mm.Hg. The skin was dry and covered with numerous petechiae. There was evidence of nasal congestion and injection of the oral pharynx. The neck was held rigidly and the Kernig and Brudzinski signs were positive. Deep tendon reflexes were hypoactive.

The initial spinal fluid was cloudy, under increased pressure, and a smear revealed gram-negative diplococci. The presumptive diagnosis was meningococcal meningitis with bacteremia and the patient

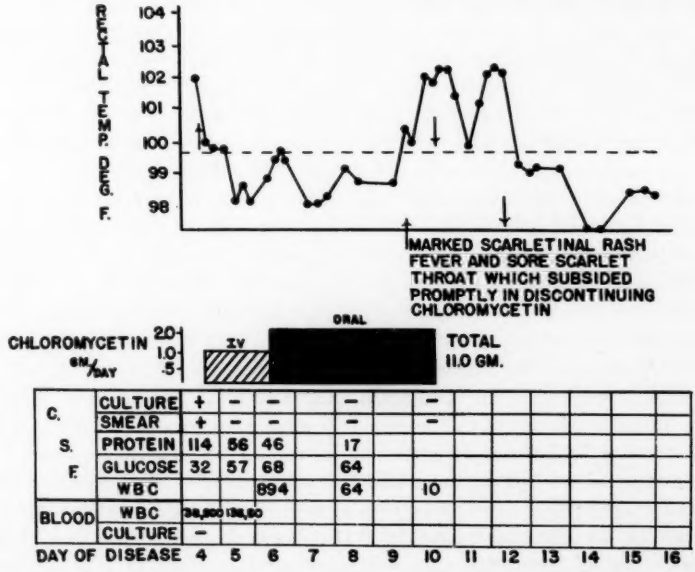

FIG. 4. Case 14. Clinical course of 4 yr. old male patient with meningococcal meningitis treated with intravenous and oral chloromycetin palmitate®. Drug reaction noted subsided promptly when drug was discontinued.

was immediately given intravenous chloramphenicol (50 mg./kg.) concurrently with intravenous infusions of salt solution and glucose. On the second hospital day the patient was begun on chloromycetin palmitate®. This was continued for a total of 5 days.

Spinal fluid cultures were positive for N. intracellularis after 12 hr. incubation. On the second day of therapy the cerebrospinal fluid was sterile and remained so. Cultures of the blood and nasopharynx were negative for N. intracellularis. Blood leukocyte counts varied between 38.8 and 17.6 thousand during the acute phase of the disease.

Clinical improvement was prompt with the temperature reaching normal levels in 24 hr. In 4 days the patient's appetite was excellent and he complained only of slight stiffness of the neck and back. On the sixth day pyrexia of 38.8°C. recurred, the nasopharynx was injected and an erythematous scarlet rash over the entire body was noted. Cultures of the pharynx, blood and spinal fluid failed to reveal meningococci. Oral chloromycetin palmitate® was discontinued and the reaction abated in 36 hr. The patient was discharged on the eleventh hospital day having received a total of 11.0 gm. of chloramphenicol (see Fig. 4). When examined in 3 mo., the neurologic examination and EEG were normal and the child was well.

Discussion

Exclusive of the tubercle bacillus, meningitis in pediatric practice is most frequently caused by H. influenzae, N. intracellularis and D. pneumococcae.[13] Unfortunately, penicillin, sulfadiazine and streptomycin are not uniformly effective in each of these types. Sulfadiazine is remarkably curative in meningococcal meningitis.[14] It exerts some favorable influence upon the course of pneumococcal meningitis,[15] and plays a minor role in the management of H. influenzal meningitis.[16] Penicillin is relatively ineffectual in patients with H. influenzal meningitis. In sufficient dosage this antibiotic is effectual in meningococcal meningitis and is the drug of choice in pneumococcal meningitis.[17] Streptomycin is of therapeutic value in H. influenzal meningitis but not in the other types. The synergistic action of various drugs has been established, such as the combination of streptomycin, sulfadiazine and hyperimmune serum which lowered appreciably the mortality and course of illness in H. influenzal meningitis.[5] Penicillin used jointly with sulfadiazine has provided the best results in the management of pneumococcal meningitis,[18] although the fatality in this virulent form of meningitis remains in the neighborhood of 40%. Dowling and his coworkers[19] have noted an antagonistic influence when aureomycin and penicillin are used concurrently in patients with pneumococcal meningitis.

Chloramphenicol, administered as the sole form of therapy in H. influenzal meningitis, has produced quite favorable results.[1,2] In over 100 patients, this antibiotic has equaled or improved upon the previous therapeutic achievements obtained when streptomycin, sulfadiazine and hyperimmune rabbit serum are combined. In 30 or more patients with meningococcal meningitis, chloramphenicol produced excellent results without fatality. These findings have not improved upon the excellent achievements of sulfadiazine in meningococcal infections. Nevertheless, in the patients treated with chloramphenicol, there has been rapid abatement of the meningitis and, in addition, patients with the clinical picture of fulminant bacteremia recovered following administration of this antibiotic.

There are no published results pertaining to the use of chloramphenicol in pneumococcal meningitis and it is presumed that the patients here reported represent the first recorded cases. The authors have treated four adult cases of pneumococcal meningitis with chloramphenicol.[7] In two patients treated during the early stages of their disease, there was rapid amelioration of meningeal signs with uneventful recovery. In two patients first treated late in their illness, fatality ensued even though in one there was complete clearing of the invading pneumococcus from the blood and spinal fluid. The fatal outcome in the

two patients was attributed to the pre-existing cerebral damage rather than to the infection per se which was actually brought under control.

In managing meningitis, every effort should be made to establish a specific diagnosis as promptly as possible. Furthermore, it is vitally important to institute prompt correct therapy as early as possible in order to forestall the development of irreversible changes to the surface of the brain which may ultimately lead to a localized infection and focal collections of fluid in the subdural space. Chloramphenicol, an antibiotic of broad range, provides the therapist an opportunity to institute treatment as soon as a definite diagnosis of pyogenic meningitis has been made. As already emphasized, the spinal fluid should be promptly examined in order to detect the causative organism. If pneumococci are observed, therapy might well be supplemented with, or changed to penicillin, according to the judgment of the physician since present evidence does not permit chloramphenicol to be compared with penicillin and sulfadiazine in this type of meningitis. The authors' preliminary results in pneumococcal meningitis appear encouraging but warrant further clinical testing before any conclusions are permitted. Streptococcal meningitis has been successfully treated with chloramphenicol[20] and this antibiotic is effective in human staphylococcal infections.[21] The value of a therapeutic regimen which requires one antibiotic is therefore obvious.

Chloromycetin palmitate® is a notable addition to the armamentarium of the pediatrician. This orally administered antibiotic is capable of maintaining therapeutic concentrations of chloramphenicol in blood and spinal fluid when employed in the dosage of 150 mg./kg. daily, administered usually on an eight hour schedule. Children and infants have tolerated this antibiotic remarkably well without attendant nausea and vomiting. No serious side effects were noted and the antibiotic was not discontinued because of aberration in the hematologic picture or renal condition. Platelet or blood leukocyte depression was not observed.

Recent reports have provoked alarm relative to chloramphenicol and its depressing reaction upon the hemopoietic system. Fatal cases of aplastic anemia are said to have resulted from its use[22-24] and granulocytopenia is likewise reported.[25] After the chemical nature of chloramphenicol became known its potential hazard for the hemopoietic tissues, by virtue of its nitrobenzene structure, was realized.[26]

The clinical experience of the present group working in collaboration with investigators of the Army Medical Service Graduate School, Washington, D.C., includes therapy of more than 600 patients ill with varied acute infectious diseases. Observations upon the hematologic status, in these patients, were made prior to and following the administration of this antibiotic. Adverse blood reactions attributable to the drug were not observed nor was medication discontinued because of leukopenia, granulocytopenia or anemia. Chloramphenicol is a valuable antibiotic for the treatment of specific acute infectious diseases and not for minor ill defined illnesses. Its promiscuous use, as with many potent drugs, is unwarranted.

Conclusions

Twenty-three patients with pyogenic meningitis were treated with chloramphenicol as the lone form of therapy. Chloromycetin hydrochloride was employed intravenously in 12 cases during the early stages of infection and chloromycetin palmitate® was employed as maintenance therapy. In 11 cases, oral chloromycetin palmitate® was used exclusively. This palatable form of chloramphenicol was well tolerated and produced measurable concentrations of antibiotic in the blood and spinal fluid. Of 23 patients treated, 22 recovered

completely and one died. The fatality occurred in a critically ill child first treated on the eighth day of disease. Of the 22 recovered patients, 12 had meningitis caused by H. influenzae, 8 by N. intracellularis and 3 by D. pneumoniae.

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SPANISH ABSTRACT

Tratamiento de las Meningitis con Palmitato de Cloromicetina Resultados Terapéuticos en Veintitres Casos Pediátricos

Los autores trataron 12 niños con meningitis por bacilo hemófilus influenza, 8 casos por meningococo y 3 por neumococo. Sus edades variaron de uno a 48 meses, con promedio de 19. Todos estaban severamente enfermos, y presentaban todos los signos y síntomas típicos de meningitis. Aún cuando 9 de ellos habían recibido antibióticos previamente todos tuvieron cultivos positivos del líquido cefalorraquideo.

Se uso clorhidrato de cloramfenicol intravenoso en aquellos casos comatosos o con vómitos, a razón de 50 mlgs. por kilo de peso, como dosis inicial. A las 6 horas, se dió la ¼ parte de la dosis inicial y así se continuó cada 6 horas por todo el tiempo que las condiciones clínicas del enfermo no permitían usar la vía oral. Tan pronto como esto fué posible se administró palmitato de cloromicetina a la dosis de 150 mlgs./kilo y por día en 19 casos, y 100 en otros 4 casos dividida cada 6 horas. Once de los enfermos recibieron exclusivamente palmitato desde un principio.

Previamente habían usado estas dosis en sujetos normales y se habían encontrado niveles en la sangre de 10 a 30 gammas por c.c. y de 5 a 15 en el líquido cefalorraquídeo. La administración intravenosa en los pacientes seriamente enfermos y con vómitos fué muy útil pues se obtuvieron rápidamente altas concentraciones de antibióticos en sangre y líquido espinal. El antibiótico se suspendió a los 5 ó 7 días después de que los enfermos se hicieron afebriles siempre y cuando los cultivos de líquido cefalorraquídeo ya fueran negativos y la pleocitosis hubiera mejorado francamente. La duración promedio del tratamiento fué de 12 días. Todos los enfermos curaron con excepción de uno de ellos.

Con este plan terapéutico los niños con meningitis por hemófilus influenza y meningococo dieron cultivos del líquido cefalorraquideo negativos respectivamente a las 33.6 horas y a las 27.4 horas de iniciado el tratamiento, y los de meningitis neumocócica hasta los 3 días. Solo un caso de meningitis por hemófilus influenza tuvo cultivo positivo y fué el niño que falleció. Con excepción de este enfermo, la temperatura se hizo normal a los 2.1 días de la terapia sin tener relación alguna con la severidad del cuadro, edad del enfermo o germen aislado de la sangre o líquido cefalorraquídeo. El estado general mejoró mas rápidamente aún, pues dentro de las primeras 24 a 36 horas ya se hacía francamente evidente, la cefalea duró no mas de un día y a las 24 horas los enfermos podían tomar la medicación por vía oral.

Sólo 4 enfermos desarrollaron colecciones subdurales que se descubrieron durante la primera semana y cuyo tratamiento se hizo por punciones subdurales repetida y extirpando las membranas.

El único caso fatal desarrolló hidrocefalia interna. Su enfermedad se descubrió hasta el octavo día de evolución y la terapéutica especifica se instituyó cuando ya existía gran cantidad de exudado acumulado en el espacio subaracnoideo. A pesar de tratamiento enérgico que incluyó la administración intraventricular de estreptoquinasa, murió a los 7 días de iniciada la terapéutica.

Los niños toleraron el antibiótico muy bien sin que tuvieran vómitos o náuseas, no tuvieron leucopenia ni trombocitopenia.

El cloramfenicol usado exclusivamente en el tratamiento de las meningitis por hemófilus influenza ha producido en otras manos resultados favorables, si no mejores cuando menos iguales, a los obtenidos combinando estreptomicina, sulfadiazina y suero hiperinmune de conejo. Asímismo, en la meningitis meningocócica también da excelentes resultados; aunque no mejores que los logrados con la sulfadiazina, la cloromicetina produce una rápida mejoría del cuadro y aquellos enfermos con bacteremia fulminante curan con este antibiótico. En lo que respecta a la meningitis neumocócica, tratada con cloromicetina, no hay relatos en la literatura, pero aunque los casos curados por los autores son escasos, los resultados son halagüeños. Las meningitis estreptocócicas también han sido tratadas con éxito con cloramfenicol y dicho antibiótico también es efectivo en las infecciones estafilocócicas humanas.

La cloromicetina que es un antibiótico de amplio margen de acción, da al terapeuta la oportunidad

de instituir tratamiento tan pronto como se ha hecho un diagnóstico definitivo de meningitis piógena. Si resulta ser neumocócica, la cloromicetina puede ser suplementada con penicilina o usar ésta exclusivamente de acuerdo con el criterio del médico, ya que por el momento no se pueden comparar los resultados obtenidos con cloromicetina con los de la penicilina y sulfadiazina en las meningitis neumocócicas.

Los autores insisten en que deben realizarse todos los esfuerzos por establecer un diagnóstico específico lo más pronto posible pues es de importancia vital instituir una terapéutica correcta temprana para evitar o impedir el desarrollo de cambios irreversibles en la superficie cerebral que determinen una infección localizada y colecciones focales de líquido en el espacio subdural.

29 South Greene Street

PLEUROPNEUMONIA ORGANISM MENINGITIS COMPLICATING RUPTURED MENINGOCELE

Report of Case with Recovery

By JOSEPH H. DAVIS, M.D., AND LAWRENCE H. ARNSTEIN, M.D.
Palo Alto, Calif.

THE role of the pleuropneumonia group of organisms in human infections is still being clarified, and only two previous reports of the isolation of this organism from the central nervous system have come to the authors' attention.[1,2] The following report concerns a meningitis developing in an infant with a meningocele, the latter having ruptured at the time of delivery. Culture of the spinal fluid demonstrated the pleuropneumonia organism, and recovery followed treatment with oxytetracycline (terramycin®).

REPORT OF CASE

Infant G. G. was born at the Palo Alto Hospital at full term following an uncomplicated pregnancy. Birth weight was 2.5 kg. Infant was found to have a sacral meningocele covered with a thin dural membrane which ruptured during delivery. Physical examination was otherwise normal. There was no evidence of sensory or motor impairment. A temporary closure of the defect was affected when infant was 3 hr. old, and he was started at once on prophylactic penicillin 100,000 u., and streptomycin 0.125 gm. each every 12 hr. Surgical repair of the meningocele was accomplished on the 5th day of life. The sac was opened, nerve roots freed as much as possible, half the sac excised, and the rest infolded so as to accomplish a complete dural closure and to save as much of the sac as possible. Lumbo-dorsal fascia from both sides was doubly imbricated over the dorsal closure. Skin overlying the defect, being quite thin, was closed with difficulty, and later broke down in part necessitating local applications of saline and Dakin's solution packs in preparation for a plastic repair.

Penicillin and streptomycin were continued, and except for a slight fever on 1st postoperative day, infant remained well until 26th day when there was a sudden elevation of temperature to 38.8°C. (Fig. 1).

Lumbar puncture had been done on the 10th day, and spinal fluid revealed 200 white cells/mm.^{3} with 89% polymorphonuclears and 11% lymphocytes. Spinal fluid protein was 162 mg./100 cc. Puncture was not repeated until 29th day when white cell count was 3047/mm.^{3} with spinal fluid protein 280 mg./100 cc., chlorides 570 mg./100 cc. and sugar only 3.5 mg./100 cc. Two days later cell count was 6.8 thousand with 98% polymorphonuclears. Smear and culture were repeatedly negative for ordinary bacteria, but examination of sediment revealed small gram-negative pleomorphic bodies suggesting the presence of the pleuropneumonia organism. This was confirmed on 2 occasions using the following criteria to establish identification of the organism:

1. Typical colony morphology. 2. Intense staining with Dienes and Giemsa stains. 3. Inability to move the growth on plates with a loop or needle as pleuropneumonia-like organisms grow into the medium and are difficult to remove. 4. Growth only on a highly nutrient medium to which has been added horse serum. Animal inoculation studies were not carried out.

Because of fever, penicillin and streptomycin were stopped on 31st day of life and replaced with terramycin. (Triple sulfonamide therapy was used for a brief transition period, but this was probably unimportant.) Initial dose of terramycin was 0.1 gm. every 4 hr. (about 200 mg./kg./day). Within 18 hr. after starting terramycin, temperature had returned to normal. After 1 wk. dosage was reduced to 0.05 gm. every 4 hr. On 41st day of life, 11 days after starting terramycin, patient's general condition and appearance of wound were both satisfactory enough to allow the skin defect to be repaired.

From the Palo Alto Clinic and the Palo Alto Medical Research Foundation, Palo Alto, Calif.
(Received for publication Sept. 2, 1952.)

BABY G.G. – SACRAL MENINGOCELE WITH RUPTURE AT BIRTH AND MENINGITIS DUE TO PLEUROPNEUMONIA ORGANISM

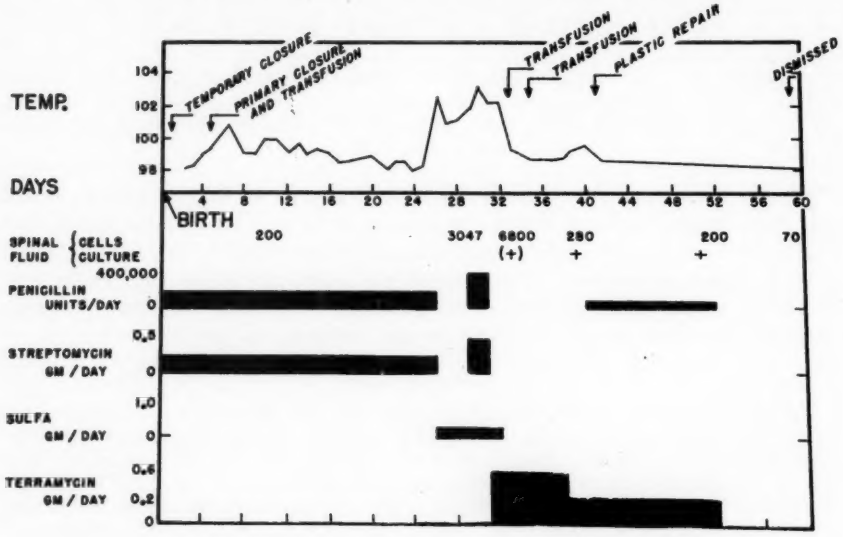

FIG. 1

Terramycin was given for a total of 21 days. Penicillin, 100,000 u./day, was also resumed at time of the plastic repair. Temperature remained normal. Spinal fluid cleared, and infant left the hospital at 2 mo. of age. At that time weight was 3.9 kg. and head measured 38 cm. in circumference. At the time of this report he is 15 mo. of age; weighs 9.5 kg., measures 76 cm. in length, and has a head circumference of 45 cm. He is able to sit and can support himself in a standing position, but does not yet pull himself up. Anal and vesical sphincters have functioned normally; there has been no sensory loss, weakness, paralysis or spasticity of lower extremities. Skin over the sacral defect has remained intact, and there is no bulge. Anterior fontanel has not closed completely, optic discs are normal, and recent skull films show no separation of sutures. Although motor development has been slow, it is felt that recovery has been complete and progress good.

DISCUSSION

The surgical problem involved in the repair of meningocele and spina bifida has been described and the results of Penfield and Cone,[3] which were secured in the pre-antibiotic era, are still enviable. They operated on 21 cases with but two deaths, and no cases of post-operative hydrocephalus. Chambers[4] reports 10 cases with one death (due to infection) and 2 cases with subsequent hydrocephalus.

The pleuropneumonia group of organisms has been isolated from various animals with a number of types of infections including arthritis in rats, respiratory infections in mice, and in cows, etc. A general review of the subject has been made by Sabin.[5] The organism has been found frequently in the human genital tract both male and female, and its pathogenicity has been suggested in cases of Reiter's disease, arthritis and colitis. A group of cases of arthritis were found[6] to have pleuropneumonia organisms on prostatic and cervical culture, and these disappeared after treatment with aureomycin.

The first reported[1] case of the pleuropneumonia organism involving the central nervous system was in a 20 year old male who suffered a penetrating wound of the orbit, and subsequently developed a brain abscess and meningitis. The patient failed to improve during treatment with sulfonamide drugs and penicillin, but recovered after the abscess was drained and streptomycin was used locally and systemically. The organism was initially sensitive to streptomycin but became resistant during therapy.

The other report[2] is that of a 5½ year old boy with cyanotic congenital heart disease who developed signs of meningitis which were found while in the hospital under treatment with sulfonamide drugs and penicillin. Pleuropneumonia organisms were isolated from both blood and spinal fluid. He was treated later with streptomycin as well as penicillin. A cerebral abscess and meningitis were found at autopsy.

The pleuropneumonia organisms are small and pleomorphic, difficult to recognize on smear, and difficult to culture. It is probable that their presence has been overlooked in the past in cases of sepsis, meningitis, etc. In view of the reports of prevalence of the organism in the male and female genital tract, it seems likely that in the present authors' case the organisms could have gained entrance to the central nervous system through the ruptured meningocele at the time of birth. The penicillin and streptomycin therapy apparently inhibited growth for a time until the organism developed resistance to these drugs, at which time it was still sensitive to terramycin. The authors were unable unfortunately to secure sensitivity studies on the organism against the various antibiotic drugs, but aureomycin has been reported effective in the literature, and terramycin worked well in this case.

Summary

A case of meningitis due to the pleuropneumonia-type organism occurred in a newborn infant with a spinal meningocele. The source of infection is believed to have been from the maternal birth canal through the dural membrane which ruptured at birth. The infection became apparent after 25 days of penicillin and streptomycin therapy, but responded promptly to terramycin, and the baby made a complete recovery from the infection.

Acknowledgment

The authors wish to express their appreciation to Mrs. John Harris and Miss Mary Przybyla, laboratory technicians, for the initial recognition of the pleuropneumonia organism in this case, to Dr. William Kuzell and his staff at the Stanford University School of Medicine for culturing and finally identifying the organism, and to Dr. Robert Berner of Palo Alto for the plastic surgery in repairing the skin defect.

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SPANISH ABSTRACT

Meningitis por Gérmenes de la Pleuroneumonía como Complicación de un Meningocele Roto

Relato de un Caso con Curación

Se trata de un niño que nació con meningocele del sacro cubierto por una delgada membrana que se rompió durante el parto. Fué operado temporalmente horas después y se le puso en penicilina y estreptomicina profilácticamente. La corrección quirúrgica se hizo al quinto día; la piel cerró con dificultad y posteriormente se abrió, pero excepto por febrícula el primer día postoperatorio, estuvo bien hasta el vigésimo sexto día en que comenzó con fiebre alta. La punción lumbar reveló proteínas muy altas, glucosa muy baja, pleocitosis por neutrófilos muy intensa y la presencia de cuerpos pequeños pleomórficos que eran gram negativos sugiriendo la presencia de los organismos del grupo pleuroneumonía. Al vigésimo primer día se suspendió la penicilina y estreptomicina y se le dió terramicina, aproximadamente 200 mlgs/Kg/día, que abatió la fiebre a las 48 horas. La droga se dió así por 7 días y la mitad de la dosis por 2 semanas más aunque a los 11 días de su principio el estado general del niño y el de la herida eran satisfactorios y se reparó el defecto de la piel.

A la edad de 15 meses ya se sienta, se queda de pie, su perímetro cefálico es de 47 cm., funcionan normalmente sus esfínteres y no hay trastormos neurológicos de miembros inferiores.

En vista de la predominancia de estos gérmenes en el tracto genital, se cree que la vía de entrada en este caso fué a traves de la rotura de la membrana del meningocele en el momento del parto.

300 Homer Avenue

STAPHYLOCOCCAL PNEUMONIA AND EMPYEMA

By ABRAM KANOF, M.D., BERNARD EPSTEIN, M.D., BENJAMIN KRAMER, M.D., AND IRVING MAUSS, M.D.
Brooklyn

IN A previous paper[1] the authors discussed the clinical picture and characteristic pathology of staphylococcal pneumonia. A high mortality characterized the disease at that time. The role of sulfonamide drugs[2,3] in reducing this mortality has been reported on favorably by some but has been questioned by others.[4-8] All reports agree that penicillin has greatly reduced the death rate.[9-12] In the present paper it is proposed to point out the changes in management and in mortality brought about by the use of the new agents, particularly aureomycin.

In the first series, the cases of staphylococcal pneumonia were classified as primary or bronchogenic, and as secondary to staphylococcal septicemia. One of the most dramatic changes is the almost complete disappearance of the septic type of staphylococcal pneumonia. In the present series of 41 patients, 30 are of the primary type. Eleven cases are secondary, not to staphylococcal septicemia but to chronic debilitating disease such as fibrocystic disease of the pancreas. Lacking the factor of septicemia, the syndrome of the pneumonia *per se* is similar in patients of both groups.

CLINICAL ASPECTS

Diagnosis: The diagnosis of staphylococcal pneumonia has become more difficult since the introduction of the new therapeutic agents. In the previous series, the diagnosis was established by isolation of the specific organism from the blood or empyema fluid during life, or from lung abscesses at necropsy. As already indicated, however, the cases associated with staphylococcal septicemia have practically disappeared. Empyema, as we shall see, is less frequent, and when it does occur it may clear up without paracentesis, offering no opportunity for culture of the fluid. Finally, more frequent recovery has made the opportunity for postmortem examination in this condition infrequent.

In the absence of specific bacteriologic findings, diagnosis of this disease depends almost entirely on clinical criteria. The authors have attempted to establish such a picture by correlating the clinical and bacteriologic findings in the patients of the first series and also in some of the patients of the present series. The factors in this clinical picture consist of the age of incidence, the manner of onset, the development of typical complications and, of primary importance, in the roentgenologic picture. The clinical picture is summarized in table 1.

ROENTGENOLOGY

Any single one of the roentgenologic changes may occur with other pulmonary conditions. However, the combination of parenchymal infiltration with atelectasis, abscess formation, empyema, pyoneumothorax and bleb formation constitutes a unique picture, especially when it occurs in the first months of life. Infiltration in a single lobe may be

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TABLE 1

SIGNIFICANT FEATURES IN CLINICAL PICTURE OF STAPHYLOCOCCAL PNEUMONIA

Age	Less than 3 mo.—30 cases
	3–12 mo.—6 cases
	over 1 yr.—5 cases
Classification	Primary: 30 cases; symptoms of pneumonia after pharyngitis
	Secondary: 11 cases; symptoms of pneumonia complicating
	a. fibrocystic disease of pancreas..... 4 cases
	b. chronic purulent skin infection..... 2 cases
	c. chronic staphylococcal septicemia..... 2 cases
	d. leukemia..... 1 case
	e. suppurative cervical adenitis..... 1 case
	f. prolonged diarrhea..... 1 case
Onset	Acute: 17 cases; rapid onset of fever, dyspnoea, cyanosis and pallor
	Insidious: 20 cases. Fever slight or absent
	Catastrophic: 4 cases; sudden onset of acute symptoms plus those of pneumothorax
Fever	Nine patients had no fever, others had elevated temperature curves which followed no distinct pattern
Pulmonary manifestations	Infiltration in all cases (100%)
	Abscess formation in 19 cases (48%)
	Empyema in 23 cases (57%)
	Pneumothorax in 15 cases (38%)
	Bleb formation in 10 cases (25%)
	Atelectasis in 7 cases (17%)
Cardiac manifestations	Myocardial failure in 5 cases
	Pericarditis in 1 case
	Bacterial endocarditis in 1 case
	Myocardial abscess in 1 case
	All 8 patients died.
Other manifestations	Diarrhea in 8 cases
	Acidosis in 4 cases
	Abdominal distention in 8 cases
	Staphylococcal peritonitis in 1 case
	Abscess of kidneys in 2 cases
	Purulent meningitis in 1 case
	Brain abscess in 2 cases
	Osteomyelitis in 2 cases
Hematologic changes	ESR moderate to marked increase in 36 cases; normal in 5 cases
	Hemolytic anemia: 35 cases;
	Polymorphonuclear leukocytosis: 38 cases
	Normal WBC count: 3 cases

the initial change, or the disease may begin with a diffuse, sometimes bilateral bronchopneumonia. This was observed in many patients when chest roentgenograms were available soon after the onset of symptoms. The development of parenchymal abscesses followed the infiltrative stage at varying intervals, sometimes appearing on the initial roentgenogram but more often appearing later. In the present series abscess formation was encountered in 9 primary cases and in 10 patients with secondary staphylococcal pneumonia.

The diagnosis of pulmonary abscesses was made by roentgen examination in 13 patients, and in six of these postmortem confirmation was obtained. In six additional patients the diagnosis of pulmonary abscess was made only at postmortem examination. The roentgenographic identification of pulmonary suppuration requires sharp images, and it was

found that exposures made at 1/60 sec. are necessary to prevent interference from respiratory motion. Films with varying degrees of penetration may be required to demonstrate foci of necrotization through infiltrated lung, and erect and lateral recumbent views for the demonstration of fluid levels may be necessary. As a rule intrapulmonary abscess formation in these cases of staphylococcal pneumonia was multiple. The abscesses were sometimes closely clumped together, often with satellite abscesses scattered diffusely through other pneumonic foci. Their cavities varied in size from almost imperceptible necrotic lesions to excavations of considerable size. The larger abscesses, particularly when situated at the periphery of the lung close to the axillary margin were difficult to differentiate from encapsulated empyema. The abscesses usually occurred within areas of pulmonary consolidation and represent areas of degeneration within patches of focal pneumonia. No definite lobar or lobular pattern was found. The degree of infiltration usually was greatest in the vicinity of the abscesses, but necrotization with very little surrounding infiltration was not uncommon. Frequent roentgen examinations revealed changes indicative of healing of the abscesses as the condition improved. Not infrequently, recession of infiltration and abscess formation occurred in one area while advancing parenchymal involvement with tissue break-down appeared elsewhere in the same or the contralateral lung.

Empyema occurred in 57% of the present group of patients, compared with 87% noted in the series reported previous to the use of sulfonamides and antibiotics. In 11 patients the empyema fluid was free in the pleural cavity and in 11 others it was encapsulated. In 8 patients the empyema was extensive, filling the pleural cavity so that the entire lung field was obliterated on the roentgenogram. In 12, the exudation was less extensive, involving about half the chest field. In 3 patients, only a small amount of purulent fluid was present in the chest.

Empyema occurred in the right pleural cavity in 15 patients, and in the left in 8. In 11 cases, empyema was present when the child was admitted to the hospital, and in 2 others it developed within 4 days after admission. In 5 patients, it was a late development. At times, considerable difficulty was encountered in evaluating the extent as well as the location of the fluid within the pleural cavity.

Pneumothorax occurred in 11 of the patients treated without aureomycin, and only once in the 12 patients treated with this drug. In 7 cases, air was found in the pleural cavity before either aspiration or any other surgical procedure was attempted. In the remaining 5, it followed chest aspiration. The degree of onset of pneumothorax was variable; in some children it developed insidiously so that the time of onset could not be ascertained and its presence was not suspected before roentgen examination. In others it was associated with severe respiratory distress and cyanosis. In 4 cases, relief of intrathoracic pressure by emergency thoracentesis or the insertion of a rubber catheter into the pleural cavity with subaqueous drainage was required. As a rule, a variable amount of fluid was noted in the chest indicating a hydropneumothorax. Small areas of encapsulated pneumothorax situated at the periphery may be difficult to distinguish from blebs.

The development of emphysematous blebs in children with staphylococcal pneumonia is an interesting, unique and frequent phenomenon. It occurred in 10 cases in the present series, and in one patient the bleb was so large as to simulate a large pneumothorax. As a rule, the appearance of the blebs is not accompanied by any remarkable clinical change, and they usually receded gradually as the patient recovered. Differential diagnosis from abscess may be difficult, but the appearance of blebs late in the disease during the phase of recovery helps in establishing the diagnosis.

In three patients atelectasis of varying degrees was present roentgenologically. In four additional ones focal areas of atelectasis were encountered.

The beneficial effects of antibiotic and chemotherapeutic agents on the course of staphylococcal pneumonia are reflected in the changing roentgenographic manifestations of the disease. Prior to the advent of the sulfa-group of drugs, the roentgenology of the chest revealed a progressive, extensive and rapidly changing picture of parenchymal infiltration and necrotization, accompanied by empyema and pneumothorax. The disease pursued a long, indolent and frequently fatal course.

When penicillin was added to the therapeutic regimen, the roentgenographic picture of staphylococcal pneumonia became more benign. The rapidly changing picture of parenchymal infiltration and destruction slowed perceptibly. The widespread extent of abscess formation appeared to diminish, and the shortened clinical course of the disease was reflected in the greater speed with which the lungs resumed their normal appearance. When aureomycin was added to the treatment another tendency appeared. Rather than the widespread suppurations seen in the earlier series, or the more closely grouped and rapidly responsive lesions seen with sulfa and penicillin treatment, the lesions treated with aureomycin added to the other agents had a tendency to remain confined to one lobe, and its immediate vicinity.

The clinical course observed in the later group of patients was one of shorter critical symptoms, restricted anatomic involvement, and rapid recovery. However, it should be emphasized that the roentgenograms during and after the phase of clinical recovery often showed considerable parenchymal infiltration, and it has been deemed advisable not to depend on clinical findings alone, but to continue treatment as long as the roentgenograms show pulmonary pathology.

Treatment and Prognosis

The authors' experience with the various therapeutic agents is tabulated in table 2.

TABLE 2

Mortality in Staphylococcal Pneumonia Treated with Various Agents

Agent	No. of Cases	% Mortality
None	37	73
Sulfonamides	17	50
Penicillin plus sulfonamides	16	25
Aureomycin plus penicillin	12	0

Treatment of Empyema

Many authors[2,9,10,13–15] have emphasized the need for thoracotomy or subaqueous drainage in the treatment of empyema, and some of the patients in the present authors' first series were treated by these methods. Other authors[16,17] have obtained good results by repeated aspiration followed by instillation of penicillin into the empyema cavity. The present authors have obtained good results by this method, and with aspiration alone if the patient was receiving large doses of oral sulfadiazine and intramuscular penicillin. Chart 1 gives the clinical details in seven patients with empyema who were treated without surgical intervention.

CHART 1

CASES OF EMPYEMA TREATED BY ASPIRATION AND SULFONAMIDES AND/OR PENICILLIN

Name	H.Gel	S.K.	H.G.	Br.F.	M.A.	M.B.	Ph.P.
Age	1 mo.	1 mo.	1 mo.	1 yr.	2 wk.	2½ mo.	1 mo.
Type of pneumonia	Primary	Primary	Secondary	Primary	Primary	Primary	Primary
Type of empyema	Encap.	Encap.	Encap.	Free	Free	Free	Free
Size of effusion	Moderate	Moderate	Moderate	Large	Moderate	Small	Large
Description of pus	Creamy	Thick	Thick green	Seropurulent	None	Thick	Thick
No. of taps	2	8	1	2	1	1	5
Total am't pus extracted	5.0 cc.	7.5 cc.	0.25 cc.	327.0 cc.	None	5.0 cc.	Small am'ts
Subsequent procedures	None	None	None	None	None	None	None
Pneumothorax	None	Secondary slight	None	Secondary marked	Primary moderate	Primary moderate	Secondary moderate
No. days of fever after taps	Afebrile	1	3	25	0	1	4
Total no. days fever	Afebrile	7	15	28	3	2	16
Intrapleural medication	None	Penicillin: 50,000 u. 7 instillations	None	None	None	Penicillin: 50,000 u.	Penicillin 25,000 u. 5 instillations
Antibiotic therapy	None	Intrapleural penicillin only	None	None	Penicillin: 200,000 u. daily for 8 days	Penicillin: 40,000–50,000 u. daily for 8 days	Penicillin: 100,000 u. daily for 7 days; 200,000 u. daily for 15 days
Chemotherapy	Sulfadiazine	Sulfadiazine	Sulfapyridine, sulfamethylthiazole	Sulfathiazole	Sulfadiazine	None	None

CHART 2

CASES OF EMPYEMA TREATED WITHOUT DRAINAGE

Name	M.F.	L.C.	A.P.	A.G.	R.P.	S.S.	S.R.
Age (mo.)	2½	1½	1	2½	1	15	3
Type of pneumonia	Primary	Primary	Primary	Primary	Primary	Primary	Primary
Type	Encapsulated	Free	Free	Encapsulated	Free	Free	Encapsulated
Size	Moderate	Large	Large	Small	Small	Moderate	Large
Pneumothorax	Present on admission	No	No	No	No	No	No
Pulmonary infiltration	Present	Present	Present	Present	Present	Present	Present
Abscess	None	Present	Present	Present	None	None	Present
Bleb formation	None	None	None	None	None	None	None
Atelectasis	None	None	None	None	None	None	None
Temperature curve	Irregular low	Irregular low	Irregular low	Normal	Irregular moderate	Irregular high	Normal
Sedimentation rate mm./hr.	Normal	Normal	21 mm.	Normal	21 mm.	65 mm.	70 mm.
Admission Hgb.	50%	73%	74%	60%	74%	67%	63%
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered
Treatment	Penicillin and aureomycin in all 7 cases. A.P. also received small doses of streptomycin.						

Case Report

B. F., an additional patient, developed impetigo, diarrhea and finally pneumonia at 1 wk. of age. This lasted, with apparent remissions for 2 more weeks. On admission at 3 wk. of age, patient was well-nourished but pale, cyanotic and dyspnoeic. Roentgen examination revealed a pneumothorax on R side of chest with collapse of approximately 20% of lung. A few days later, evidence of encapsulated fluid was noted. Following administration of penicillin 120,000 u. plus sulfadiazine 6.4 gm. daily, she made an uneventful recovery. This patient was again seen at 4 yr. of age. Heart and lungs were entirely normal, both by physical and roentgen examination. Diagnosis of staphylococcal pneumonia had been established by the combination of typical pulmonary findings and presence of Staph. aureus 75 colonies/cc. blood.

Recovery from staphylococcal pneumonia and empyema without recourse to aspiration became common with the introduction of aureomycin. In 7 such cases, none was aspirated even for diagnosis and all cleared up on intensive treatment with penicillin and aureomycin. All 7 began as severe infections. Five of the 7 were infants under 3 months of age, and all had moderate or high fevers, all had moderate to severe anemia, and all showed a moderate or severe leukocytosis. The course in all 7 was uneventful, and the average period of active symptomatology was 7.5 days. The clinical details in these 7 cases are summarized in chart 2.

Summary

Forty-one cases of staphylococcal pneumonia, treated with sulfonamides, sulfonamides plus penicillin, and with aureomycin plus penicillin are described. Since characteristic bacteriologic findings are now uncommon, diagnosis of this condition depends on the presence of a typical clinical and roentgenologic picture, herein described.

The mortality rate with sulfonamide treatment alone was 50%. The mortality rate in cases treated with sulfonamides and penicillin was 25%. With the introduction of aureomycin none of the 12 consecutive cases in this series died.

Empyema treated with sulfonamides and penicillin often cleared with repeated aspiration alone or aspiration followed by instillation of penicillin into the pleural cavity. Cases of empyema treated with aureomycin plus penicillin seldom required paracentesis.

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SPANISH ABSTRACT

Neumonía y Empiema Estafilocóccico

Los autores relatan los resultados terapéuticos obtenidos principalmente con aureomicina en 41 enfermos con neumonía estafilocóccica. Treinta pertenecían al tipo primitivo o broncogénico y once eran secundarios a padecimientos crónicos como la enfermedad fibroquística del páncreas. Uno de los cambios mas dramáticos en esta serie es la desaparación del tipo séptico de la neumonía estafilocóccica. Asímismo, en la actualidad los casos asociados con septicemia han desaparecido practicamente.

El diagnóstico bacteriológico del padecimiento se ha hecho cada día mas difícil debido a la introducción de nuevos agentes terapéuticos y con frecuencia depende exclusivamente del cuadro clínico, incidencia, complicaciones e imágenes radiológicas.

Las características mas significativas de los enfermos fueron las siguientes: el 75% de los casos se encontró en niños de menos de 3 meses; en 30 casos se presentó el cuadro neumónico después de síntomas de faringitis, en 11 como complicación de fibrosis quística del pancreas, infección purulenta crónica de la piel, septisemia estafilocócica crónica, leucemia, adenitis supurada, y diarrea prolongada. El principio fué agudo en 17 casos, con fiebre, disnea, cianosis y palides, insidioso en 20, con fiebre ligera o ausente y en 4 de caracter catastrófico, principio súbito de síntomas agudos mas los de neumotórax. En 9 pacientes no hubo fiebre, en el resto fué alta pero sin curva especial. Las manifestaciones pulmonares fueron de caracter infiltrativo y en la mitad de los casos aproximadamente hubo formación de abscesos y empiema. Neumotórax, imágenes quísticas y atelectasia siguieron en frecuencia.

Manifestaciones cardiacas como insuficiencia cardiaca (5 casos), pericarditis, endocarditis y un absceso miocárdico se acompañaron siempre de muerte (8 casos en total).

Otras manifestaciones interesantes fueron: diarrea en 8 casos, acidosis en 4, distensión abdominal en 8 y en orden decreciente de frecuencia, peritonitis, absceso renal, meningitis purulenta, abscesos cerebrales y osteomielitis. En 36 casos hubo sedimentación sanguínea acelerada, anemia hemolítica en 35, leucocitosis polimorfonuclear en 38 y cuenta leucocitaria normal en 3.

Los resultados terapéuticos fueron los siguientes: en 37 casos no tratados con agente alguno la mortalidad fué de 73%, en 17 tratados con sulfonamidas fué de 50%, con penicilina y sulfas, en 16 casos, fué de 25% y en 12 enfermos consecutivos tratados con aureomicina mas penicilina fué de 0%.

Es interesante señalar que las lesiones pulmonares radiológicas se han modificado a medida que se han venido usando las sulfas, penicilina y aureomicina y sus combinaciones, haciendo que la imagen pulmonar de infiltración y necrotización progresiva extensa, rápidamente cambiable, acompañada de empiema y neumotórax de los casos no tratados con sulfas o antibóticos se transforme en los tratados con aureomicina en lesiones pulmonares que tienen tendencia a permanecer limitadas a un lóbulo y estructuras vecinas.

El empiema tratado con sulfamidas y penicilina a menudo curó exclusivamente con aspiraciones repetidas o seguidas de instilación de penicilina en la cavidad pleural y cuando se trató con aureomicina y penicilina raramente requirió paracentesis.

80 Linden Boulevard

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

Round Table Discussion

PROBLEMS IN CHILD PSYCHIATRY

LEO KANNER, M.D., Baltimore, *Chairman*
ROBERT J. MCKAY, JR., M.D., Burlington, Vt., and E. EARL MOODY, M.D.
Los Angeles, *Secretaries*

Chairman Kanner: Probably everybody in this audience has heard the old quip about the difference between a general practitioner and a specialist. The former, according to the jesters, knows a little about many things; as time goes on, he knows less and less about more and more, until he reaches a point when he knows nothing about everything. The specialist, in reverse, is said to know much about a circumscribed area of medicine; eventually, he knows more and more about less and less, until in the end he knows everything about nothing.

The pediatrician is the only medical man to whom this jocularly exaggerated pseudo-definition cannot possibly apply. His specialty is based not on a specific organ system or methodology but on an age group with all of its structural, functional, environmental, prophylactic and therapeutic concerns. He has thus the unique distinction of being a specialist and a general practitioner at the same time. His field is limited only to the extent that he courteously dismisses his patients when they reach the threshold of adulthood; it is broad enough to encompass every conceivable aspect of his patients' lives during infancy, childhood and adolescence.

The resulting multiplicity of interests, which is truly remarkable, has its rewards and its complications. The pediatrician has been widely accepted as a key figure to whom people turn with their puzzlements about their children's physical health, developmental pace, and mode of behavior. If a poll were taken as to whom the man-in-the-street regards as the logical adviser of parents, the overwhelming majority would undoubtedly name the pediatrician.

There is no gainsaying that such popularity must be deserved. Indeed, it is admirable how the constant progress of biochemistry, immunology, internal medicine, and the other branches of the profession is being incorporated in the instruction and practice of pediatrics on a learn-as-you-go basis.

But there is one large domain about which many pediatricians still feel quite uneasy. A few well-intentioned ambassadors of good will have toured the country in the past decade or 2, exhorting them more or less glibly to give heed to "the child as a whole," "the child as an individual," "the psychodynamics of children's behavior." It seems to me that such orations are superfluous, worthless, and to some extent offensive so long as no opportunity is offered for a much-coveted orientation in the fun-

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damentals of child psychiatry. Generalized admonitions, chapters in handbooks, articles in periodicals, even specialized textbooks are poor substitutes for actual experience.

The task of training pediatricians in the principles of child psychiatry, then, is one of the major problems which child psychiatrists and the pediatricians have in common. It may be helpful to review the situation as it has existed so far.

The community child guidiance clinics have made great contributions to the understanding of children's feelings and parental attitudes. They were set up as "teams" of psychiatrist, psychologist and social worker. Pediatricians were left out of the arrangement. Much time, effort and paper went into lengthy discussions of the exact "functions" of each constituent of the so-called team. Insult was added to injury when pediatricians, kept at a distance from all that went on in the clinics, were blamed for their alleged lack of comprehension and interest. Only recently, after about 30 years, have the child guidance clinics begun to show a desire to break through the walls of their isolation from medicine.

Four years ago, I received a letter from an official of the Division on Community Clinics of the National Committee for Mental Hygiene, requesting that I accept a capable young pediatrician who "seemed quite clear on wanting to familarize himself with psychiatry in order to use some of the basic mental hygiene understanding in his pediatric work." Even at that, the young man was viewed with some suspicion. The writer of the letter stated: "It did not seem to me that he was planning to consider himself as a psychiatrist when he finished his orientation-training; however, I may be wrong on this." I wondered about the attitude of an organization which, instead of encouraging young pediatricians, suspected as potential inposters those who looked around for a broadening of their experience.

Obviously, pediatricians could expect nothing from the pontifical attitude of the community child guidance clinics and their preoccupation with the "functions" of the "holy trinity" of the clinic team. Some few were persuaded to seek their salvation via a didactic psychoanalysis. There are people unrealistic enough to decree that every pediatrician worth his salt should have undergone a personal analysis. Aside from the matter of time and expense, the premise itself is debatable. Regardless of what an analysis will do to an individual, it can at best only serve those who submit to it as an adjunct to clinical information which it decidedly cannot replace.

Proceeding from the recognition that a children's hospital might be a better place for orientation in pediatric psychiatry than any other arrangement, Dr. Edwards A. Park decided in 1930 to have a psychiatric workshop at the Harriet Lane Home. The pediatricians thus not only could refer their problematic children to a unit in their own midst but could also, in private conferences and in staff meetings, learn something about methods of examination and treatment, observe interviews with children and parents and, above all, learn to differentiate between problems which they should be able to handle themselves and those which need specialized psychiatric attention. It was planned to have the members of the pediatric group rotate through the Children's Psychiatric Service for a minimum of 2 months as part of their general training. However, the interns could not be spared from their routine tasks entirely for this length of time, and they came to us for 3 days each week. This did not work out too well, inasmuch as they often arrived in the morning after an exhausting night on duty. The best I could do under the circumstances was to think of their own health and mental hygiene and send them to their quarters for a few hours of much-needed sleep. The war and the postwar period with the decreased availability of internes cut even this opportunity short.

Nevertheless, there are advantages in the geographic proximity. These have been symbolized more or less subtly by a phenomenon which occurred spontaneously after a pseudopodium had stretched out in 1930 from the psychiatric ameba into the Harriet Lane Home. The door between the 2 adjacent departments had always been kept locked; only the possession of a key had made passage possible. There was no community of interest between the 2 staffs. Soon after the children's psychiatric unit had been set up, the door was kept unlocked more and more frequently until the time came when a key was never needed. The door now connects, rather than separates the 2 buildings and their occupants.

On a larger scale, and figuratively speaking, the same thing happened at about the same time to the whole issue of the interdisciplinary relations between psychiatry and pediatrics. Leading pediatricians called more and more urgently for direct contact with psychiatrists who knew children and who had an eye for the child specialist's daily office and hospital practice. A few pediatricians had set out to explore the field on their own and some of them have made worth while contributions;

Cameron in England, Beverly and Aldrich in this country are names which this audience will easily recognize as outstanding examples.

A curious paradox was introduced in 1931 by Brennemann, a man whose word had a great resonance among his colleagues. In an address, entitled "The Menace of Psychiatry," he seemed to sound a shrill warning. But his blast might as well have been given the heading, "The Menace *to* Psychiatry." The seeming dissonance proved to be a healthy challenge, the call for a thorough housecleaning. Brennemann castigated the unskilled overpopularization and oversentimentalization of child psychology, the improper evaluation of certain standardized tests, the parading of obscure terminologies, and the conflicting claims of speculative, over-bearing, dogmatic "schools." All this, however, did not deter him from including psychiatric insight in the practice of pediatrics. On the contrary, he stated: "The pediatric psychiatrist, or the psychiatric pediatrician, would seem the obvious solution, and there is much evidence that he is in the making."

Brennemann's prophecy is in the process of fulfilment. There is no longer a locked door separating pediatrics and psychiatry. The twain have definitely met. And let me state emphatically that I do not subscribe to the notion that the psychiatrist is the generous giver and the pediatrician is merely a recipient who should gratefully acknowledge the donation. It is true that, in the absence of a psychiatric orientation, there is a common belief in the ascendency of the behavior symptom over unrecognized basic issues, the prescription pad is invoked to exercise the manifestations of deep-rooted anxieties, and parental perplexities are often shoved aside as irrelevant nuisances. But it is equally true that the disregard of physical factors has resulted in grave diagnostic errors, in costly and protracted "psychotherapy" delaying the early treatment of severe physical maladies, and in a blurring of the last 3 syllables of the word "psychosomatic." It is sad enough when children with tics are treated as though they suffered from chorea and kept in bed as "St. Vitus dancers," but it is equally sad when choreic patients are kept away from needed pediatric care because of a "diagnosis" of alleged "neurotic restlessness."

Pediatricians want to know what is going on in the minds of contemporary parents, teachers, psychologists and social workers with regard to children's development, behavior, needs and feelings. There is hardly a more suitable place for the acquisition of such knowledge than an active psychiatric unit functioning in a busy pediatric hospital with an outpatient as well as an inpatient division. In our clinic, it is our custom to inquire always of parents and, whenever possible, of the referring persons what they expect from us. The answers are revealing. There are those who wish to have a symptom removed and, unless our goal is explained to them, are surprised when the examiner's curiosity extends beyond the symptom. There are those who hope that, through some obscure magic called psychiatry, we change the child from something he is to a perfect little youngster in accordance with parental specifications. There are those who try to get us involved in domestic strife and expect that we make decisions for them as to whether they should divorce a spouse, evict an interfering mother-in-law, or fire a housekeeper. There are those who sense their child's struggle and their own emotional involvement and come with the sincere desire to be helped to find their way out of a blind alley. And there are, of course, many other forms of expectations, ranging from the prescription of a sedative to the child's removal from the home.

I am particularly interested in the expectations of those pediatricians who have had no opportunity to familiarize themselves with psychiatric procedures, yet have sufficient faith in them to refer some of their patients to us. I have had several such people come to me and say something to this effect: "I appreciate what your clinic has done for my patient. But would you mind telling me what it is that has been done? How did you manage to find out what the trouble was and how did you deal with it?" These questions are the expressions of an honest quest for information. In reply, I usually invite these physicians to come and sit in with our case conferences as often as their time allows. I know of none who has not responded promptly to this invitation.

Granted that such belated quests for orientation are highly commendable, still there is something singularly pathetic about them. These same people have had occasion to refer patients for major surgery. In their student years, it had been made possible for them to witness operations; they thus had a good notion of what goes on in the operating room. They did not have to go to the surgeon and wonder what he had done and how he had done it. There was no flavor of mystery about it. The same is true of referrals to the otologist, the orthopedist or the dermatologist.

The child psychiatrist is now very much in demand. I do not think that it is a feather in his hat if his pediatric colleagues send children to him in what seems often to be blind faith. I am

sure that the psychiatrist would—or, at any rate, should—be more comfortable if he knew that the referring physician, without being a psychiatrist, had an over-all notion of what is happening to his patient in the psychiatric clinic to the extent that, without being a surgeon, he has a fair notion of what happens to his patient in the operating room. This over-all notion can be obtained only through direct observation, through the concrete experience of witnessing procedures, whether they be psychotherapeutic interviews or the removal of an inflamed appendix.

But where and when was the young pediatrician to go for such first-hand experience? The community child guidance clinics, even if they had been more hospitable to him, thought and spoke in a style to which he was not accustomed. When he had his training in one of the few teaching hospitals which could boast of a psychiatric unit, his routine duties, the pressure of ward work, outpatient rush, laboratory jobs and note-taking made any meaningful contact with the unit impossible or, at best, perfunctory.

In consideration of this problem, an attempt was made to apply the Mohammed-mountain principle. If there was no way of orienting the young pediatrician psychiatrically at the source, why not bring this orientation to him at his own place of work, in the stream of his own activities? This, it was felt, had a great added advantage. Why burden the pediatrician with issues which had been referred specifically for psychiatric attention because of difficulties already in existence? Why not place emphasis on prophylaxis by helping the trainees to learn how to steer parents and children from the start in the direction of a wholesome mutual relationship? One such program was set up in a leading children's hospital and word got around that we were on the eve of a new era, the advent of what was called "the comprehensive pediatrician," one whose attitude would enable him to be a mental hygienist in the broadest sense.

The experiment, begun in 1935, met with considerable enthusiasm on the part of its sponsors. The idea as such was indeed magnificent. Here was an approach which seemed well-suited to present the needed orientation as if on a silver platter. The house officers could go on with their assignments and, while doing so, could be enlightened and guided by a competent mentor. One is therefore entitled to pause for thought about the fact that this plan has failed to take roots. In the intervening 17 years, less than half a dozen such programs were instituted, and most of these had to depart substantially from the original purpose.

One cause of the dilemma is again the hectic demand on the house officer's time, which leaves him little opportunity for matters other than immediate attention to the incessant ministrations in sickroom and laboratory.

Another cause was mentioned by Dr. Frederick H. Allen at the 1948 get-together of pediatricians and psychiatrists in Hershey, Pa. He stated that, when a person qualified to function in the described manner does go to a pediatric center, "he is confronted with a great many difficult problems that need a child psychiatrist's skill in therapy. He soon finds himself almost swamped with service cases and is diverted from the long-range goal, that of being a teacher who will enable house officers and young pediatricians to gain the kind of understanding of human beings that will make them more effective pediatricians."

A third cause has been brought home to me by pediatricians who had had their training in such a setting. After they had started out in practice, they found that they had missed in their period of instruction a chance to get acquainted with the minor and major issues of psychopathology. They came to feel that what had been intended as a guide to preventive psychiatry had its merits, to be sure, but that they had been given no help in dealing with the many behavior problems confronting them in their practice. These problems include the whole roster of symptoms centered around eating, sleeping, elimination, speech, emotional crises, scholastic progress, and tendencies toward obsessiveness, withdrawal or rebellion. They also include such puzzlements as to how to help a parent to accept the suggestion that a child be seen by a psychiatrist, how to modify pathogenic parental attitudes understandingly and tactfully, or how to evaluate, and advise parents about, a child's developmental lag.

This latter issue, about which the pediatrician is invariably consulted before any other specialist, has been sadly neglected in the years of training. As a result, the handling of the problem of intellectual retardation leaves much to be desired.

Retarded children constitute a sizable minority of the country's child population. Everyone in this audience has had to meet the problem of informing and advising the parents of such children. Allow me to enumerate some of the questions which are asked regularly with a great deal of feeling

and to which the inquirers hope to get straightforward answers, without evasion and without hedging:

What is the cause of our child's retardation? Have we personally contributed to his condition? Why did this have to happen to us? What about heredity? Is it safe to have another child? Is there any danger that our normal children's offspring might be similarly affected? How is his (or her) presence in the home likely to affect our normal children? How shall we explain him (or her) to our relatives, friends and neighbors? Is there anything that we can do to brighten him (or her) up? Is there an operation which might help? Is there any drug which might help? What about glutamic acid? What will our child be like when he (or she) grows up? Would you advise a private tutor? Should we keep our child at home or place him (or her) in a residential school? What specific school do you recommend? If a residential school, how long will our child have to remain there? Will our child become alienated from us if placed in a residential school? Will our child ever be mature enough to marry? Do you think that our child should be sterilized and, if so, at what age?

These questions vary, of course, depending on the degree of the child's retardation, on the presence or absence of other children in the family, on the parents' financial resources, on their ideas about social prestige, on their degree of acceptance or rejection of the child.

The answers to such questions have been so unsatisfactory that in the past few years parents of retarded children, grouped together in state-wide associations, have expressed their criticism publicly and in no uncertain terms. The modern pediatrician finds himself more and more under public pressure to meet the demands of parents that they give them enlightened service not only with regard to physical ills and prophylaxis but also with reference to methods of child rearing, the handling of problematic behavior, and the perplexities arising from developmental retardation.

How, then, is the young pediatrician to acquire the orientation which will be expected of him as an integral part of his professional skill?

This is the problem which I wish to submit to you for consideration at this Round Table. I should like to begin with a statement of my own, a formulation of what one might look upon as an optimal arrangement.

1. It is desirable that training on the student level offer a preliminary orientation of the kind that would drive home the concepts and facts of human development, interpersonal relations, and the satisfactions and conflicts arising in everyday living. Though the courses in psychiatry form the nucleus of such instruction, the student should be made to feel that the attitudes thus taught prevail in all other clinical departments. So prepared, the young pediatrician does not have to enter the field as a babe in the woods as far as understanding the emotional needs of his patients and their parents are concerned. While he is in the process of forgetting the memorized origins and insertions of some of the muscles of the body, he cannot possibly drop an attitude which has been instilled in him and which is solidified by his clinical experience.

2. The best and most logical mode of molding "comprehensive pediatricians" is to have "comprehensive pediatricians" do the molding. Pediatric instructors with a good psychiatric orientation would make it unnecessary to have special emissaries engaged as floor walkers in hospital wards and dispensaries. After all, it does not occur to anybody to engage a physiologist or an immunologist for the specific purpose of imbuing pediatric house officers with the fundamentals of their sciences. It is taken for granted that the pediatric instructors possess a sufficient knowledge of these fundamentals and the ability to integrate them in their teaching. Why should an exception be made of psychiatric fundamentals?

3. About 10% of the children who come to pediatricians need specific psychiatric attention. There is a choice between 3 possibilities: One is that these needs are disregarded or handled clumsily to the patients' detriment. Another possibility is that these children are sent away to be treated elsewhere; this deprives the pediatricians of valuable experience. A third alternative presents itself in the form of a psychiatric unit in the children's hospital. Such a unit should be made available to the house and attending staffs for observation, personal consultations and participation in case conferences and seminars. Thus, the pediatrician's orientation can be broadened. He can gather a first-hand knowledge of what goes on in the psychiatric workshops; he can learn much about the skill of interviewing patients and their parents; he can get an appreciation of the degree of severity of a child's emotional problem; he can become familiar with the existing methods of developmental diagnosis; he can become acquainted with the range and nature of community facilities. At the same

time, he can make a genuine contribution to the psychiatric group on the basis of his pediatric knowledge.

I realize that I am offering a model which may not be feasible in all its parts at the present time, to wit, a combination of a good psychiatric preparation in medical school, a set of psychiatrically-oriented pediatric instructors and an active psychiatric unit in the children's hospital. For the time being, compromises will have to be made because of shortage of interns, budgetary considerations, brief periods of internship which do not allow the time for rotation in the psychiatric unit, problems of office space, and instructors who themselves have had no opportunity to gain a satisfactory psychiatric orientation.

Dr. Dorothy Wyvell, Midland, Texas: We are faced with a multitude of problems because we live in such a small community. There we are faced with the problem of differentiating between the children we can help psychologically and psychiatrically and those we feel reasonably certain we can't. And of those whom we feel need extra help, many cannot afford to go the long distance whe.e good psychiatric help is available. We in this area are not psychiatrically trained to give this extra help so should we attempt to do anything at all? Would we be doing more harm than good in trying to help these people, or should we not do anything?

Chairman Kanner: There is one principle in medicine and in life generally which says that, if we can't do the best thing, we have to do the next best thing. The very fact that you are aware of the problem and feel that here is something you want to know more about, is an indication that you are not going to dismiss it as nonexistent. What with the contact you have with the families, even though you are not a psychiatrist, you can do a great deal to help. You can do "minor psychiatry." Most of the help does not come primarily from reading articles, listening to lectures, or even from wading through a textbook.

I know many pediatricians of my own generation who haven't had any of the training now advocated but who are experts on the basis of their years of dealing with children and their families. Through trial and error, they have reached an understanding and sometimes could be even helpful to some psychiatrists who deal mostly with adults and know little about children. I get people for training who come from pediatrics and people who come from psychiatry. Those who come from psychiatry do not know children. Those who come from pediatrics do not know psychiatry but are comfortable with children and learn much sooner not to be afraid of them.

Dr. Herbert L. Elias, Rockville Centre, L.I.: I would like to ask you to discuss a method or ways of advertising parents that they have a retarded child. We have been told by prominent neurologists that it is better if the parents slowly become aware of it.

Chairman Kanner: It is desirable that the parents become aware of it but it is surprising how well the parents are aware at the time when they consult someone, except that they need the additional help which makes it possible for them to accept what they have observed. I have been in the habit of consulting the parents before advising them. I ask where they place their child in terms of intelligence—what stage of development do they think the child has reached? Let us say, a particular child is 8 years old. The parents will talk it over between themselves and say, "Well, we think he has reached a stage of between 4 and 5 years." They are usually correct! Of course, they hope you will tell them that the lag is caused by this or that and is remediable but the preliminary observation is theirs. I saw recently a 9 year old child who had a general developmental level between 3 and 3½ years. The mother had been given the run-around. The parents had moved to a university town so that the child could get "speech therapy" over a long period of time, and their money gave out. They were heartbroken when they had to return home—when the child was 6 years old with a developmental level of 2 years.

Dr. Maryelda Rockwell, Clinton, Ia.: What should be done in regard to informing parents about the unfavorable diagnosis in mental retardation of the newborn when the physician has every reason to feel that the child will be a disappointment to the family and the family of very high strata?

Chairman Kanner: In most instances, this is true of mongolian children. I have found it advisable to let the parents know, if we are certain of the diagnosis. They consult us as physicians. I have told parents: "You may not be able to accept it for the time being but it is my duty as your doctor to tell you what I know."

Dr. James H. Root, Jr., Waterbury, Conn.: If you don't take a positive attitude and lead them to believe that you hope you are wrong even though you are certain you are right, how can you discourage them from spending all their money by consulting everybody else in the country about that particular thing?

Chairman Kanner: I tell them that this is what it is and we come to an understanding but I allow them, if they wish, to go on hoping that medicine will find something so long as they accept the situation intellectually and handle it practically. Time makes it possible for them to accept it emotionally as well.

Dr. Herbert I. Arbeiter, Hammond, Ind.: I would like to carry the discussion of the mongolian idiot, born in the hospital, a little further. You have told the parents and you say you will do everything you can. What do you mean by that? Is it better that this baby never come into the household because of social difficulties that it might cause, should it be institutionalized? Should the baby be institutionalized and the mother not informed? What should be done?

Chairman Kanner: These are problems which have to be dealt with individually. Much will depend on the parental reaction to your disclosure, on the presence or absence of other children, or on the availability of a place that would be acceptable to the parents.

One father called me on the phone within a week after the birth of his mongolian child. "If we take this child home," he said, " we will not be able to give him up when it is time. Can you recommend a place right from the hospital?"

On the other hand, there are parents who say to themselves, "All right, we know we have a mongolian child. We want to give him as much attention and care as we can. There are no other small children in the family; why can't we have him at home?" Well, why can't they! Some of them have read about the short life span of the mongolian child (which in my time has risen from 14 to 21 years now). They say to themselves: "If the child will die young, let us have him for that short period of time." In this situation, there is no reason for urging the parents to send the child to an institution.

Once I had a call from a physician in a small community who said a couple had a mongolian child. Could I see them immediately? These parents had not been told that they had a mongolian child. When he was 5 years old the parents were told their child was feebleminded. They developed a tremendous grudge against the doctor who was a family friend as well as their physician. I had to do a great deal of talking before I could help the parents not to start a campaign of hostility against the physician.

Dr. Alfred B. Stein, Chicago: At a meeting I attended, a letter was read from a woman at a home for mentally retarded children. In this letter she hinted that the children who had been cared for at home for a few years did better in the institution than children who had been sent there immediately. Also, it was better for the family to have these children at home for a while and to know the siblings and even for the mother, instead of dismissing this child from the time of birth.

Chairman Kanner: No generalization can be made. As I said before, each case must be handled individually. You may give the parents credit for the ability to participate in any planning, and you must consider their feelings as important as your own feelings about them.

Dr. Fred N. Roberts, Syracuse, N.Y.: One of the previous questions concerned the skilled psychiatric care in the small community. Would you care to elaborate on skilled follow-up care or convalescent homes in which these children can be placed? It has been my experience in a fairly large city that there is no place to send these children. I wonder how that is throughout the country?

Chairman Kanner: I am confronted with that problem almost every day. We still talk a great deal about the importance of early care and handling of problem children. We have hundreds of thousands of beds for psychiatric problems of adults. The number of beds available for psychotic or near-psychotic children in the whole country is still very small, entirely out of proportion with the need. This is a sad state of affairs. There are also inadequate facilities for epileptic children who would benefit from a period of hospitalization.

More and more places are opened at present, but then the question arises with regard to the ages of admission. Some will not admit a child before 6 years, some not after 10 or 12 years. I know of children who had been placed nicely to the parents' satisfaction and then, when the tenth birthday came, they had to look for another place because their school would not keep them any longer.

Dr. Roberts: In the State of New York, there are very few public institutions where a child can be sent shortly after birth.

Chairman Kanner: In the case I mentioned, arrangements were made for placement in a private home. A woman who had taken care of 2 or 3 other retarded children and become fond of them took a mongolian child and cared for him well.

Dr. Martin J. Harris, Louisville: Would you care to discuss the place of the school for the exceptional child in this plan? What type of child is best suited for that sort of institution?

Chairman Kanner: There are good schools for the child whose parents can afford to pay from $4000 to $5000 a year. I avoid mentioning those schools to parents who cannot afford it because it breaks their hearts that they cannot pay for these schools. When parents come to me I have 2 questions in my mind before talking with them: Are they prepared emotionally, and are finances available for a private institution?

Some of the expensive schools have a grand arrangement; they are proud of the units they have, sometimes 2, 3 or 4 miles away from each other. They try to fit the children so that they are congenial. They take children with various degrees of retardation and with various kinds of emotional problems. Some of the children emerge and then again others don't emerge but you know as physicians we cannot always blame the doctor or the school for things that don't work out.

Dr. Helen J. Zillmer, Milwaukee: My question is away from the management of these children but I would like to have you discuss some of the commonest "minor psychiatric" problems with reference as to how you handle them.

Chairman Kanner: This is a seemingly simple question but gives me a large order. To start with, you can't begin with symptoms because the symptom itself may or may not be an indication of a major difficulty. Much depends on the degree of the over-all disturbance. There are children who "steal" straw hats in the spring; this is just a harmless "obsessive" game indulged in by many youngsters. Again there are children who are afraid of germs, afraid to shake hands or to touch things which others have touched; there you have a serious problem of neurotic obsessiveness. There is a great deal of transition between these 2 forms of behavior. If I say "it all depends," I am not being evasive. You get the feel of the thing if you allow the parents to express themselves and learn whether you are dealing with a severe disorder or whether it is a phase that you can handle easily.

Much depends on the complaint and the way in which it is presented. Some parents come because they feel there is something about which they want your advice and your guidance. Some come with accusations against the child; other are full of excuses, trying to shove the blame on the school teacher or the school system. Nothing short of a specific knowledge of a specific problem will tell you whether you are dealing with something serious.

You pediatricians are in a better position than we are at the start; you know the family and can draw them out easily because you already know some of the background.

Dr. William H. Zavin, Portland, Ore.: How would you approach the interview of the "aggressive child?"

Chairman Kanner: There are different degrees of aggressiveness. Some is due to an organic difficulty. Some is based on sibling rivalry or on the manner in which the child has been treated at home. An accepting, permissive (though not submissive) attitude, psychotherapy through play and other projective forms of self-expression are available means of treatment.

Dr. William London, Perth Amboy, N.J.: How are we to handle the problem child who vomits and refuses to go to school—this occurs from grade to grade?

Chairman Kanner: There are children who have been insecure in their home relationships. Some time ago, a child was brought to us at 6 years of age. She wouldn't go to school; when forced, she vomited on the way to school and had to be taken home. Later, she would not leave home to go anywhere. When I first saw the child, she had very little to say. When I asked her to draw, she drew a flower. When I asked her to draw something else, she drew a boy. She said that was her younger brother Joey. Joey was the first grandson in the whole clan, who was given a great deal of attention. For the first 3 years of the little girl's life she had been fully accepted and then she was put aside when Joey came along. She drew a box—a package that Joey just got from "Uncle Ben." This was an obvious situation: the little girl did not want to leave home in order to give Joey the field completely. When the parents understood this clearly and sought to remedy the situation, the child had no difficulty the following fall in attending school.

Before we continue the discussion, I should like to make a few general remarks. There are essentially 4 types of parents who come to us. The majority come because they want help. They see a difficulty but do not know what type of help they want. They may want the removal of the symptoms or immediately bring in their own involvement: "*I* have difficulty with my child," and so forth.

Then we have the "take-us-over" type of parent: "You tell us what to do and we will be good patients; lead us and we will do everything you say."

Then we have the "make-him-over" type of parent: "I can't stand him the way he is, I bring him to you and you make him perfect so he will always obey, go to bed when I want him to, and always have excellent marks in school."

Then there is the openly hostile parent: "I have tried every mode of punishment and it didn't work; you know something about these things and you probably know how to punish him; you tell me how to punish him most effectively."

We live, as far as children are concerned, in a transitional period. We have left-overs from the old-country authoritarian type of child rearing, when the predominant feature was the acceptance in the culture of parental autocracy. "Mother knows best—daddy can use a strap." There was a time when this sort of child-rearing was needed. In cultures where the child grew up to be a "subject" of the government and was to submit unquestionably to the rules of state, church or soldiery, he had to be trained from the beginning to be submissive or it would be bad for him.

In the last 2 decades, when the child was "discovered" to be an individual in his own right, the pendulum often swung in the opposite direction: You must never say no to a child, a child must live out his personality (at the time when he does not have a fully developed personality). This concept led people to turn the home over to infantile autocracy. In many instances, however, we deal with a tug-of-war situation. You pediatricians are familiar with the pattern: One small child on one side and 2 or more adults on the other, both having their own weapons. All the child has to do is refuse to eat or to go to bed. The adults have the power of dragging the child up to bed or threatening him at meal time. All of this is called "negativism" on the part of the child and "methods of discipline" on the part of the parents.

But, fortunately, in the average family we have real democracy at work in the home, with the child considered as a novice in this business of living, much as an intern is considered as a novice in the business of medicine. An intern cannot go and wouldn't want to go without "discipline"—that is, somebody showing him how to do things.

A child needs guidance. When he stumbles in his first attempts at walking, everybody sees something wonderful in this stumbling. He is trying to walk but hasn't quite made it. But when he stumbles in matters of personal relationships, in learning to know what he wants and what he doesn't want, "what is accepted and not accepted," then the issue of "obedience" and "discipline" comes up and the same people become indignant and don't see this as a step forward in finding his place in the family circle.

Parents are people, most of whom are well adjusted, some of whom are less well adjusted, and some of whom are poorly adjusted. The poorly adjusted parents are not villains. They are people who, themselves, need sympathetic understanding and help.

Dr. William Kiser, Jr., Atlanta: On the subject of how the practitioner can be helped with psychiatry —I have sat in with groups, real experts in the practice of medicine, and they may not use some of the psychodynamic work but they have assets of a very warm heart. I have felt that giving a lot of technical explanation of why the child does these things explains away all the complaints. It doesn't mobilize the assets of any of the doctors in the group. Some people who have been in practice for a long while are pretty good; they may not call it psychotherapy but they put out warmth to the family in trouble.

Chairman Kanner: At the meeting yesterday, a woman spoke up and said that she was practicing in a small community and had no access to a child psychiatrist, that she, herself, had no specific psychiatric orientation. As she related what she did, it was evident that that particular pediatrician had pulled herself up by her own boot straps, had learned from her own experience and, not being able to do the best thing in all situations, she does the next best thing.

Dr. William L. Venning, Charlotte, N.C.: These psychologic problems in practice kind of remotivate people. I think that as far as pediatricians and physicians interested in children are concerned that is the big problem with us; how are we going to motivate ourselves? Because one cannot possibly do any good work in child psychiatry or child psychology unless he has a real basic interest in human beings.

If a man has a sincere interest in human beings, with a few simple technics in handling the problems of the patients, it doesn't take long to find out that people are hungry for spiritual help. We need to be able to recognize the severe psychiatric problems, it is true. Just recently I had a 4 year old schizophrenic patient; I had seen one before and fortunately knew there was no use in my handling the problem and sent the child along. But by and large, the problems that you want us to

help with are problems in the realm of the spirit. Most of us have been trained in science alone and very often, if you adopt the scientific attitude, you frequently will lose out on the spiritual side of the picture.

In my own practice if I know the parents are disturbed and the child's situation is such that his complaints are due to the parent, I have found it helpful to suggest that, if they wish it, I will be glad to give them an evening appointment. If they keep the appointment and you just let them talk, they will give you the clue to the simple problems.

Chairman Kanner: Is there any sharp distinction between what you call spiritual help and scientific help?

Dr. Venning: I always think of scientific pediatrics as that type of pediatrics which excludes the human relationships with the patient—being satisfied with the cure of specific organic disease and a set of laboratory data, excluding the feelings of the patient and parent. We all agree that pediatric psychiatry is scientific but the distinction for the practicing pediatrician is that anybody can treat pneumonia whether the patient likes you or not or whether you like the patient. But when Mrs. Smith brings Johnny in with a problem of temper tantrums and several other behavior disorders, if you are not spiritually and humanly interested in helping that woman, I don't care what you do, you cannot help her.

Chairman Kanner: Your basic ingredients are, then, the scientific diagnosis you have made and the desire on your part to help Johnny. What is it then that makes you hesitate? There are a number of things: your own feeling that there is an element of time that you have to consider; your own feeling that, once you get into it, you might strike a hornet's nest and be involved without any possibility of going any further.

Dr. Venning: There is also the feeling that, if you talk too soon, you will miss out on the opportunity of hearing the whole story and may miss the crucial point.

Chairman Kanner: It depends on what you say prematurely. If you say: "You are a rejecting mother!" "You have driven your child to obsessiveness or you have overprotected your child, shame on you!" "You are neglecting your child!"—if you proceed in this manner, you won't have a chance to say anything else. If you invite the parent to talk about herself for a while, being a sympathetic listener, then you can help the parent feel that, even though you are the child's physician for his physical needs, you are also interested in his total welfare. You will find, in most instances, appreciation of the interest and a wedge which will give an opportunity for discussion.

Dr. R. F. Goddard, Albuquerque, N.M.: When I arrived in New Mexico, I found that there was no child guidance clinic even in the whole state. We instituted the only mental hygiene society in the state, in our county. We have meetings and discuss the various problems we encounter in our individual practices. In areas where these are no facilities set up, our experience could be helpful in organizing groups to utilize the experience of the individuals among us with psychiatric training. This is set up on a voluntary basis; we all donate some time and feel that in about a year we can go to the state medical society and get them to approve groups as associations with mental health programs. This includes a plan to gradually obtain for ourselves the necessary money to have a full time psychiatrist in the area to whom we can send severe cases for help.

Chairman Kanner: That is certainly a beginning of something which offers promise.

Dr. E. Earl Moody, Los Angeles: Would you differentiate between the theory that the child is born to behave in a certain pattern and the attitudes that make up the personality of the child, the attitudes of the environment?

Chairman Kanner: You mean the difference between the notion that the child will always behave in a certain manner because he was "born that way"?

Dr. Moody: Yes.

Chairman Kanner: I don't believe, really, that anybody nowadays holds that a child steals a quarter from his mother's pocketbook because he was destined to do this. There are certain inherent things which we bring along with us: some people are born to have certain color eyes, some are born to be taller than others, others to be shorter, etc. But we have learned something in the last few decades. In earlier times, emphasis was put on what was called inherent personality structure; most of the earlier studies were based on that sort of an attitude. Then a new school came along and said: It is all environmental conditioning. Its chief proponent said: "Give me any child at the beginning and, through conditioning, I will make of him a custom built genius or criminal." The work of the child guidance clinics brought in another important consideration. They began to ask: What is it on the outside that influences the child? They began to occupy themselves with the ob-

servation and study of the principal effect of parental attitudes and communal attitudes on the development of the individual child.

Now we have come to a point when it is no longer a question of environment or heredity but a question of how these things blend and fuse and integrate.

Dr. Dorothy V. Whipple, Arlington, Va.: I think what we are really discussing is the impact of the new knowledge of psychiatry on our conscience. It may well be that pediatricians may be the first source where society gets this impact. However, no matter how psychiatrically minded we pediatricians may be we have a problem that is far larger than it is possible to cope with. We have to have the assistance of the entire community. All the other institutions and people having to do with children must be psychiatrically minded to go to the doctors, and treat children with understanding. We can't do it alone but can help people who are pretty normal people—young couples who are reasonably well adjusted and who come into us with problems more or less on the superficial level. We must discuss the technics of breast feeding, toilet training and behavior problems and we must help a great many people to avoid developing problems. Then we see the ones we can't handle. We see them grow up and the problem going along and developing. It is quite beyond us to really solve it. Some of them perhaps need intensive psychiatric treatment. Almost no community has the facility for that intensive psychiatric treatment. If we are ever going to have the knowledge of psychiatry translated to the entire population it has to be done, not only through us, but through a great many other agencies. It has to get down even to the level of the individual person. Using an analogy is never particularly good but I have 2 analogies that I think are particularly good. Time was when bacteriology was only in the hands of the medical profession. Now it has gone way beyond that and the population is bacteriology conscious on the individual family level. The same thing is true of nutrition: at one time it was only the medical profession who knew of proteins, etc.; now the general population hears of this every day. Now we have to get to the people themselves these personality questions. In the long run it has got to come from the schools and on a lay level.

Chairman Kanner: Well, all I can say is that no truer words have ever been said!

Dr. Leo J. Flax, Denver: In our mental hygiene clinic the set-up is one in which the psychiatric social service worker meets for interviews with the parents and the child psychiatrist meets with the child. Where, in your opinion, would a pediatrician fit into that situation?

Chairman Kanner: There is definitely a place in the community for the social worker, for there are things that only the social worker can do. The social worker has much more time for the parent than the pediatrician can devote to interviews. I don't believe that at any time the pediatrician should be left out of the picture and I think I have made a very strong point of it.

Dr. Flax: How does he get into the picture?

Chairman Kanner: He won't be able to get into the picture as it is now constituted, that is, as the guidance clinic is now set up.

Dr. Goddard: Would you discuss the autistic child?

Chairman Kanner: Autistic children are those who withdrew at an early age from the ordinary contact and relationships with human beings. Certain features are so typical that, when a 4 year old autistic child is brought to the clinic for the first time, my secretary comes in and tells me that there is an autistic child in the waiting room,and she is usually right.

These children show no particular troubles for the first few months of life and then the parents notice that there is something that isn't developing in the ordinary way. When they go to the crib to pick the child up, there isn't the anticipatory reaction that the ordinary child shows. He lies there like a sack of flour. When the parent comes home, the child does not run towards him. He does have good contact with objects. As time goes on, the parent is disturbed because the child does not respond to verbal address. The first suspicion is one of deafness. Then the intellectual endowment is questioned.

These children can work puzzles very well. They can build things with blocks, develop phenomenal memories. Some of the patients remain so withdrawn that they never develop verbal communication at all. These children will visit a relative at the age of 2 or 3 and not return to that house until 8 or 9 years and know immediately where things are and what to go after. If a child like that came into this room he would investigate the ash trays, etc., but show no awareness of a human being in the room.

In addition to the withdrawal there is also a particular kind of obsessiveness. They do things over and over again.

Why do these children withdraw? This is an exceedingly difficult question to answer. In fact, I

don't have a ready answer. We did find a number of features in a majority of children. In the family, we have often detached, obsessive parents who are autistic people grown up "successfully" in certain respects. Quite a few of them are in *Who's Who* or in *American Men of Science*. I have a collection of books published by the parents or grandparents of my autistic patients. They are successful scientists, artists, executives, etc. They are, to all outer appearance, well-mated couples in the sense that there are fewer divorces in the group with autistic children than in the general population. Also there are few instances of domestic strife; as a matter of fact, they respect each other in a way that 2 unrelated people respect each other. They are serious-minded and literal-minded, often to the extreme.

In bringing up their children, they carry out all the rules and regulations but the child is put away like a car is put away in the garage, and by the time he is expected to communicate, he is away from the world that hasn't been brought to him.

I have seen a small number of autistic children who have warmhearted parents but for some reason have been kept isolated for a period of time.

Physically, these children, all of them, are pictures of health. The EEGs that have been done are normal, although I did have one patient who had convulsions.

Question: Does this child eventually develop into a schizoid personality? One that the pediatrician should not try to deal with?

Chairman Kanner: Schizoid is a mild term. They are withdrawn and share this withdrawal with the schizophrenic person. I have seen children who have had 3 or 4 years of reasonably satisfactory adjustment before they became schizophrenic. If we want to call autistic children schizophrenic, we should at least realize that they are a special group. In their later development, some emerge and others remain in extreme withdrawal. We have seen a few adults who had started out as autistic children; they are peculiar and withdrawn but they have never had any delusions or hallucinations.

SPECIAL ARTICLE

PILOT STUDY OF CHILDHOOD ACCIDENTS: PRELIMINARY REPORT

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A major problem of child health today is the prevention of accidents. Part of the answer to this problem lies in the answer to the question of why some children have more than their share of accidents. Although there is an extensive literature on the accident-susceptible or accident-prone adult, there has been but little written on this aspect of the accident-prone child. Much remains to be done in order to identify the respects in which children who have repeated accidents differ from their fellows. In spite of the lack of reported studies of children there has been a tendency to talk about the accident-prone child and to attribute to him the personality characteristics and motivations seen in the adult accident repeater. It was with a desire to do something about it, and not merely to talk about it, that the study, of which this paper is a preliminary report, was begun at the Babies Hospital of the Columbia-Presbyterian Medical Center, New York, in the fall of 1951.

The purpose of this investigation was to explore methods for identifying and determining the significance, in relation to the incidence of accidents in children, of parental attitudes, parent-child relationships, environmental accident hazards, personality characteristics and functioning of the child, physical coordination and physical disabilities as these are reflected in the experience of the accident repeater. It was planned to do this through the study of a relatively small number of children of school age and their environment, both personal and physical, comparing a group who have had repeated accidents with a group who have no accident history. Even though the number of children studied would be small some questions might be answered. In addition, leads for further investigations with a larger number of children might emerge. In any event, it would be discovered whether the proposed approach in the study would bring out meaningful information.

The plan was to select for investigation 10 or 12 children of average intelligence who had been brought to the Emergency Clinic of the Columbia-Presbyterian Medical Center for treatment of accidental injuries at least 3 times during the 18 month period prior to the outset of the study. Children whose only accidents had been traffic or who had had severe or repeated head injuries were to be included. The children to be studied would be from the hospital neighborhood since there is no ambulance service. They were to be between 6 and 11 years of age, taking care to eliminate older children who might have started their physiologic adolescent changes. These were to be compared with an equal number of children of similar age and sex who had been followed earlier in the Well Baby Clinic of the Pediatric Service, who had no accident history and whose health history had been good. The suggested ratio was 9 boys to 3 girls since this corresponded roughly with the child-accident fatality figures.

Each child was to be given a careful medical history and physical examination. Neurologic examinations would be done by a member of the Neurological Service especially assigned for this purpose. Similarly, ophthalmologic studies were to be carried out in the Eye Clinic by a member of the department especially delegated. Electroencephalograms would be done on all children. We

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planned to evaluate the general motor co-ordination of the children in the physical and neurologic examinations and, in addition, attempted to devise some crude measures of coordination in which differences in motor skills might be observed. No well standardized tests of co-ordination seemed to be available. Three situations were planned: (1) several trials at hammering a nail of specified size into a piece of soft pine, (2) sawing through a piece of soft pine of uniform size and (3) piling toy building blocks on end. In all of these some rough quantitative comparisons could be made between children.

Psychologic studies of the child included the Stanford-Binet and Wechsler Intelligence Scale for Children, Bender Gestalt, Projective Drawings, Rorschach, a specially devised sentence-completion test containing items of accident import, and the Thematic Apperception Test. Four extra pictures bringing in accident situations were added to the Thematic Apperception Test plates. (These were prepared by Mr. W. Graham Cole of the Metropolitan Life Insurance Company.) In this battery of clinical psychologic tests are included those of mental measurement, personality diagnosis and evaluation.

Anamnestic data about the child were to include a general and personality developmental history, behavioral adjustments, relationships with people, child and adult, in- and outside the family circle, school progress and adjustment, play and recreational interests and activities. This is such material as would be included in the background story in a clinical psychiatric appraisal of a child. In addition attention would be paid to the nature and attendant circumstances of any accident.

Several clinical psychiatric interviews were planned with each child employing a combination of verbal, play, drawing, etc., activities as modes of communication. The usual things looked for in psychiatric interviews with children would be covered including his general adjustment technics, his ways of meeting with new and difficult situations, his relationships with significant persons, his interests, his hopes, his fears and ambitions. It was planned to pay particular attention to the child's exposure and reactions to known factors increasing accident hazard and to explore diligently his emotional reactions before, during and after his accidents.

Study of the family setting would consist of a psychiatric social investigation by an experienced psychiatric social worker. This would include personality data concerning the parents, the patient, other children and other people in the home. The interrelationships among the members of the family, their attitudes and feelings toward each other, their patterns of adjustment, as well as all material and observations usually included in the background history of a child under psychiatric study, would be surveyed. Special attention was to be paid to the accidental injury patterns of all members of the home and to the type of supervision the child received in his play activities. An accident-hazard appraisal of the home was planned. If possible some appraisal was to be made of the neighborhood play facilities.

Contacts with the schools were planned as a part of the general appraisal of the child.

The plan for action outlined above can be recognized as including the usual kind of study given a child who is brought to a psychiatric clinic for children, a study which utilizes the services of the child psychiatrist, the clinical psychologist and the psychiatric social worker. In addition, investigations by the pediatrician and other medical specialists are included in the survey of these accident-repeater and accident-free children.

The investigation was conducted by the staff of the Pediatric Psychiatric Clinic of the Babies Hospital with the addition of an experienced psychiatric social worker especially employed for this project. The psychiatric interviews with the children and general physical examinations were carried out by 2 child psychiatrists, both of whom have had extensive pediatric background; one of them has had well-rounded psychoanalytic training.

The selection of cases posed more problems than we had anticipated. The Emergency Clinic nurses were well aware of the "What, you here again" child but no routine record of accident patients was kept. The hospital record room filed the cases under anatomic diagnoses. Spotting the accident-repeater children was finally accomplished through 4 means: (1) the charge nurse of the Emergency Clinic keeping a list of child patients of appropriate age; (2) a similar list kept by the clinic aide in the minor surgical clinic; (3) a watch on admissions to the children's surgical ward; (4) reference to the record of accident cases in patients accompanied to the hospital by a police officer. These last were accidents which had occurred on the streets, in the parks or playgrounds or at school where some city liability might be involved. After this search 20 cases were located in children between 6 and 11 years of age having 3 or more accidents following Jan. 1, 1950 (we finally extended

the period to cover 21 months before Oct. 1, 1951). Of these 18 were boys and 2 girls. Several of these children had a long string of visits back to the preschool years but were continuing to have accidents. We noted a number of children who had had several accidents prior to January 1950 but only 1 or 2 since. It has been noted that accidents do tend to drop off in frequency after the 5 to 6 year period but we were frankly surprised to find so few children meeting our criteria. Data on the frequency of nonfatal accidents in children are rather scarce. However, in the *1951 Accidents Facts* a table, "Student Accidents by Type and Grade," gives some information which seems pertinent. This table covers over 27,000 reported accidents requiring a doctor's attention or causing absence from school for a half day or more. The over-all frequency for school and nonschool accidents was 15.3/hundred thousand student days in the kindergarten through grade XII range. This survey covered a 9 month school year. Computation would give one accident/32 children or, if it is assumed that the accident rate is 3 times greater in boys, one accident/16 boys and one/48 girls. The criterion for an accidental injury as requiring a doctor's attention would be similar to our definition. Birnbach in a study of accident repeaters and accident-free children in a junior high school population of 600 boys found 55 children meeting his criteria for 5 major accidents; his definition was an injury causing one or more days' absence from school. These 55 children had a total of 364 accidents during their school careers. This would be an average of 6.6/child, or about one/year. He could find only 48 who were completely accident-free. There would seem little doubt as to the fact that we are dealing with a real group of accident repeaters in our study, representing one extreme of the scale.

Of our group of 20 children 9 were finally included in the study, 8 boys and 1 girl; the girl was the younger sister of one of the boys. We were unable to get in touch with 4 children. Four mothers were working and unable to bring the children in, one of these was also of the impression that her child was not having many accidents. One mother was not interested in participating as her 11 year old boy was not having as many accidents as in his earlier years. The other mother was so tied down by her responsibilities to her large brood of children that she could not give us the necessary time. One child was excluded after study was well under way because his intellectual level was below the average range. The 9 children studied ranged in age from 6 years, 2 months to 11 years, 6 months when first seen; the youngest child was the girl. A total of 47 accidental injuries had been treated in the Emergency Clinic. Nineteen of these had occurred in the home; in only one child had all the accidents occurred at home. Twenty-eight had occurred outside the home. Every child had had at least one in the home. Many of the accidents which appeared in the hospital records antedated the time selected for determining the suitability for this study. Most of the children had had numerous lesser injuries for which they had not been brought to the hospital. The list of injuries included 7 fractures, 1 suspected but not proved fracture of the nasal bones, 4 dislocations and 17 lacerations requiring suturing.

The selection of the nonaccident group of children was difficult. It was finally decided to select the children from the camp lists of the Babies Hospital Medical Social Service Department. These families had had contacts with the hospital and there was held out the possibility of another camp experience. Since we wanted essentially healthy children there was little we could offer the parents for their participation in the study aside from our gratitude and a thorough examination of their children. The final selection included a younger brother of one of the accident repeater boys. The ages of the 9 nonaccident children ranged from 7 to 11 years, with the youngest being a girl. Two brothers of decidedly different temperaments from the same family were also included in the nonaccident group. The children with no history of accidents would seem to be a group from the opposite extreme of the accident scale.

Both groups came from the same neighborhood. The accident group included 7 Roman Catholic, 1 Protestant and 1 Jewish child; the nonaccident group, 7 Roman Catholic and 2 Protestant. (Those accident cases not studied included 9 Roman Catholic, 1 Protestant, 1 Jewish.) The income level of the 2 groups was similar, ranging from $32.00 to $60.00 a week, with one family in which both parents worked achieving $85.00 a week.

The average number of visits required to complete our studies was 12 with a maximum of 15 and a minimum of 9. The nonaccident cases on the whole took fewer visits. The parents of the children were most co-operative in keeping appointments. It is felt that the relationship established with the psychiatric social worker was important in maintaining the good will and participation of the families.

Before discussing even in a preliminary way the findings of this investigation it would seem

well to examine briefly what others have thought of the problem of accident proneness, particularly in childhood. Melanie Klein stated that her analytic work with children had convinced her that recurrent accidents represented attempts at suicide with as yet insufficient means. Ackerman and Chidester noted a certain reckless abandon in play. They believed that accident-prone children have more fear and more unexpressed hatred and guilt feelings than the average child. They attribute to "accidental" self injuries the basic motives of hurting the self out of guilt or symbolically hurting others out of revenge or a combination of both. They describe in some detail a child who was a patient at the Southard School; the self injuries in this child represented an expression of anger at the mother, and self-punishment for sexual phantasies about which she felt guilty; there was considerable secondary gain from the injuries themselves. Fabian and Bender discussed the predisposing factors in 65 children with histories of head injuries admitted to the children's psychiatric service at Bellevue Hospital. None of this group had epilepsy, psychosis or central nervous system disease; 33 had a history of 2 or more major accidents. The highest number of accidents was in the 5 to 6 year period. Marked psychopathology was noted in the parents; alcoholism in the family was a factor in 27 of the 65 cases. They believed that the combination of a sadistic father and passive masochistic mother was important and that in young children the accidents represented inverted aggressive gestures directed at the frustrating adults. The most characteristic profile of the children was of sado-masochistic behavior patterns. Identification with the sadistic father or with the aggressor were other features and at times depressive states leading to self-inflicted injuries. Siblings of the patients observed reacted to the severe family psychopathology either with the accident habit or with behavior disorders. Follow-up studies revealed that many of the children carried their accident proneness over into adult life. Fabian and Bender realized that their conclusions might have limited significance since all of the children had been referred because of behavior disorders, and they appreciated also that post-traumatic sequelae in the head-injured child might influence the psychologic factors elicited; they hoped to stimulate general hospitals to elucidate the problem of predisposition to accidents with social and psychologic investigations. Bakwin and Bakwin in a short paper review the scant literature on children. Following Dunbar's ideas about adult accident repeaters they stress the role of over-authority in the home and the resulting pent-up aggression and resentment in the child. The Bakwins include no cases of their own in the paper.

In 1948 2 studies of accident repeaters in circumscribed groups of children were published. Birnbach compared the performance of 55 accident repeaters and 48 accident-free boys in a junior high school population of 600 on a pencil and paper personality inventory scale, the National Safety Education Tests, the New York State Physical Fitness Standards for Boys and the Rogers Strength and Physical Capacity Tests. The accident-free group showed a superior knowledge of safety, better home and emotional adjustment, and were more dependable, industrious and co-operative. The accident repeater group showed superior gymnastic skill, greater crude strength and indications of home, health and emotional maladjustment. Certain additional observations were made of the children in the school situation and through interviews. One fifth of the accident repeaters came from broken homes and 18% reported at least one strict parent. The accident repeaters tended to be aggressive and to dominate social relationships by physical means; they were poor losers and on the whole were grandstanders in sports. These children tended to react to the stress of adjustment demands with impulsive behavior. Rebelliousness tended to emerge when frustrated or under emotional strain. They were interested in sports and activities which required a large degree of muscular effort. Difficulties in concentrating were common.

Fuller reported a most interesting study of the accidents in a carefully circumscribed nursery school group. She noted that, while the injury rate in 2 year olds is about equal in the 2 sexes, as the children grew older boys got hurt more often than girls although the injury rate for the whole group declined. Young children do seem to learn to keep out of trouble! The children with highest injury scores all seemed to have difficulties in harmonious group living although they showed few behavior characteristics in common. A suggestive correlation was found between frequency of injury and a variety of attributes: exceptional physical strength, a dare-devil attitude, emotional reactions easily aroused, impulsive or unreflective behavior, a rude or insulting attitude to others, especially adults, and in girls, tomboyishness. Fuller's conclusions were most tentative and the need for further studies was stressed. Fuller and Baune published a sociometric study of a second grade class in which the injury rate was 5 times as great as in any other class in the same school. In general the less popular children received more injuries than did the socially accepted group; a few children

ran counter to the general trend. This study provides suggestions for further investigations of injury proneness as a group as well as an individual problem.

Dunbar's studies of accident proneness in 1600 fracture patients have received considerable attention and many of her conclusions have been applied to children. The age range of her cases was from 12 years on up. She noted a tendency to impulsive behavior under stress particularly in relation to authority. The accident-prone patients were characterized by a jerky, restless tension, a good-fellow role in social relationships, a tendency to make up their minds definitely and quickly and to focus on immediate rather than long-range goals. They tended to have accidents when strong aggressive hostility was aroused or pressure from authority became too great. Aggressiveness then breaks out in an impulse to punish himself and those responsible for his frustration. She noted that at least one parent had been reported as "strict" in the vast majority of the accident repeaters. Strictness, a difficult term to define, was regarded as actions or attitudes in the parent which would produce "a feeling of severe insecurity (being involved), because parents are cruel or unapproachable." She adds that an ill parent might produce such a feeling in his offspring. The relationship with a strict parent is regarded as the source of the authority-hostility conflict. Dunbar also noted a history of accidents in the families of 40% of her cases, and that 90% had had a strict religious upbringing. She found that in 80 to 90% there was some specific worry in the life situation preceding the accident. The initial reaction following injury was one of guilt with emphasis on destruction of others or of themselves. The injury was apt to be regarded as punishment for wrongdoing and the patient might express the idea that he deserved the accident. This was quickly repressed and there followed a concentration on the injury itself.

In general the term "accident-prone" would seem to imply a certain purposiveness, or motivation toward accidental injuries. The dictionary definition of prone as "mentally inclined or disposed, or bent; propense, apt—usually in a bad sense as prone to evil," does not seem to imply purposiveness. However, in present-day dynamic psychiatric thought much of human behavior which is apparently unmotivated or "happenstance" is regarded as being unconsciously motivated. It would seem important not to confuse the psychologic use a person makes of an illness or injury once it has occurred with motivation to fall ill or to inflict self injury. Certainly it is not at all uncommon for children to look on illness as punishment for misdeeds. One catches a cold because he did not obey mother and wear his rubbers or the cold goes on to pneumonia because he failed to take care of himself. In looking over the information we acquired on the 2 groups of children we have tried to take into consideration not only the possibility of motivated injuries but also the possibility that the child might find himself in predicaments where injury was inevitable. *A priori* it seemed feasible to consider possible factors involved in repeated accidents under these 2 general headings:

Individual Motivation: (1) guilt problems with self punishment, atonement, or anger turned back on self; (2) recapture of love with atonement, stimulation of a protective response in parents, attention; (3) revenge, especially against parents through punishing them; (4) riddance of painful tension; (5) emulation of older sibling; (6) increased self-esteem through group acceptance, taking risks to show how courageous or grown-up he is, injuries signifying a badge of courage; (7) thrill of danger, "fusion of pain and pleasure"; (8) great curiosity which happens to bring child into hazardous situations.

Other than Individual Motivation: (1) defective control over emergency emotions, or overpowering emergency response; (2) impulsivity, inability to inhibit, victim of a whim; (3) hyperactivity, "constitutional," usually involving clumsiness or secondary to anxiety; (4) inability to grasp potential danger in situations as learned from past experiences; (5) inadequate control and education, parental and others; (6) environment which is especially hazardous; (7) chance environmental circumstances.

Any conclusions to be drawn from this study of 9 accident repeaters and 9 nonaccident children must be tentative. The group is small and not susceptible to statistical analysis. This is a preliminary report of progress and a great deal of the material, especially from the psychologic test battery has not yet been carefully analyzed. We can say with assurance, however, that the approach has given us a great deal of usable information. We can understand on the basis of our observations the kind of child with whom we are dealing, his family, and factors which have contributed to his present status. Some of the information would seem helpful in evaluating the accident habit or in understanding why a child does not have accidents. All who have been concerned with the investigation feel strongly that any conclusions reached thus far must be applied to accident repeater children in general with great caution.

Our groups of children certainly represent 2 extremes on the accident scale. They are, however, exposed to the same neighborhood environmental hazards and attend the same schools. They are comparable in intelligence as measured by formal tests; Accident Repeaters—Stanford-Binet I.Q. range 85 to 155, average 114, W.I.S.C. I.Q. range 85 to 126, average 104. Nonaccident—Stanford-Binet I.Q. range 81 to 139, average 112, W.I.S.C. I.Q. range 79 to 120, average 103. The children in both groups did not impress any of the study staff as being seriously emotionally disturbed to the degree of the children usually seen in the Pediatric Psychiatric Clinic. The accident group has a high percentage of Roman Catholic children; this holds for all of the children who were considered for the study. The children with repeated accidents seen in the Emergency Clinic came, with 3 exceptions, from an area of poorly repaired, dilapidated tenements with inadequate play space and recreational opportunities. This particular neighborhood area has a high percentage of Roman Catholic residents. It was of interest that although children with isolated or occasional accidental injuries came to the Emergency Clinic from both this slum area and an adjacent neighborhood equally accessible to the Medical Center, only 15% of the children with repeated visits were from the better housing area. It is thought that this probably represents an increased accident hazard in the poor housing neighborhood. The homes, however, of our nonaccident group were also in the poorer area.

We shall attempt to summarize the findings of the various examinations to date and to indicate trends where analysis of the data is not yet completed.

Little of significance was turned up in the physical studies. General physical examinations revealed but few abnormal physical findings. Children in both groups were healthy and free from gross defects. The accident children showed scars of old minor injuries, and in most of them fresh bruises and scratches were observed.

Neurologic examination was completely normal in all of the accident cases except in one boy who showed a minimal impairment of skilled movements. Of the nonaccident children 2 showed slight clumsiness in succession movements, one pseudoathetotic movements of the outstretched hands, one an absence of associated arm swings, and another a drift of the left hand with an equivocal Babinski on the left. These findings in 5 of the nonaccident children were minimal and were not thought to be indicative of central nervous system disease.

Ophthalmologic examinations revealed normal visual acuity in all but one of the children of each group. One nonaccident child was myopic and one accident child had diminished visual acuity in one eye due to an old corneal scar resulting from an injury. The same boy had some fusion difficulties. Two of the nonaccident children had mild fusion difficulties. All other children had normal muscle balance and both groups showed normal depth perception.

The electroencephalograms are more difficult to evaluate. Only one child showed "normal" findings throughout; he was the oldest of the accident group. Five of the accident and 6 of the nonaccident children had basically normal records; 2 from each group were borderline; 1 from each was classified as abnormal. One accident case had a mildly irregular record. Only 1 of the children showing questionable neurologic signs showed any EEG irregularity, a nonaccident child with borderline findings. All the nonaccident children showed abnormal responses to hyperventilation; 6 of the accident group were described as abnormal, 2 borderline and one normal. The significance of these EEG findings is not clear. The records were looked on by the interpreter as not being usual ones for children in this age group. None of the abnormalities was of the type seen in convulsive disorder. The findings, however, do not differentiate between the 2 groups of children.

Evidences of mixed laterality were suggestive in 2 of the accident children and 4 of the comparison group.

Gross estimates of coordination in the general physical and neurologic examinations were of normal motor coordination. In the coordination tests described above there was little to choose between the performance scores in the 2 groups when each child was compared with his age mate. A difference was noted in the approach of the children to these tasks. The accident children tended to hammer or saw in a less controlled and cautious manner than the nonaccident children.

There were a fair number of hospital admissions for infections (otitis media, pneumonia, adenitis, 1 poliomyelitis) in the accident group. These were not seen in the nonaccident group but these children had been selected on the basis of a good health history. The accident children were not significantly free from illness; Dunbar has reported that her patients with repeated accidents had a low incidence of disease.

Both groups of children were well aware of dangerous and potentially dangerous situations. The

nonaccident children in their daily lives managed to keep away from them whereas the accident children did not. Seven of the nonaccident children had had some accident prevention education at home; insufficient information is available on the other 2. Of the accident children information about accident education at home is available in 5 instances; 3 children were given some instruction by their parents, 2 were not. Insufficient information is available about the school accident education programs of the nonaccident children to allow any conclusions. The mother of the same 2 children who received no home training reported that none was given at the school. Three accident-case parents went over the accident hazard check list with their children.

The accident group of children and their parents showed a markedly casual attitude toward the injuries. One mother was fatalistic and felt that "accidents just happen." The children tended to take care of minor cuts and scratches themselves without turning to their parents. The hospital records indicated in at least 10 of the accidents surprising lapses of time between the injury and arrival at the Emergency Clinic. A boy was brought in for inspection of a lacerated hand which had occurred a month previously and had pretty well healed without infection. A child with a fractured clavical was brought in 2 days after her fall. Another patient with an eye injury with moderately severe bleeding came in 5 hours later. A boy who stepped on a nail came in one week later for medical attention. In the group studied the factor of secondary gain from the injury would not seem to be important.

Two of the accident children and one of the nonaccident children came from broken homes. Epilepsy was reported in the family histories of 2 children, one from each group. The father of the brother and sister in the accident group was alcoholic as was the father of 2 boys, one in the accident and one in the nonaccident group. The mothers of 5 of the accident children worked outside the home; only one of the nonaccident mothers was employed; as an apartment house superintendent she was around the house most of the time. The most striking findings had to do with the incidence of accidents in other members of the immediate family and in the collaterals. Accidents occurred in other members of the immediate family in 7 of the 9 accident cases and in only 3 of the nonaccident families (one of these was the family which also provided an accident child to the study). Accidents occurred in the collateral family lines of 8 of the 9 accident cases and in only 2 of the nonaccident group (one of these was the same family which had a child in each group). Some of these families had rather lurid accident histories. A maternal uncle of one of the boys was killed in a fall out of a window at 3 years of age. His paternal grandfather died of injuries sustained in an elevator crash. A paternal aunt was struck and killed by a car at 24 years of age. A paternal uncle was seriously burned as a child when he pulled a vat of boiling water over on himself. A paternal aunt lost 2 children through accidents; a baby choked to death on something given it by another child while outside in the carriage and an 8 year old boy died when a glass mantle, dislodged by people dancing overhead, fell on him as he was doing his homework. The boy's father as a child was struck on the head by a thrown can of milk which became imbedded and had to be pried loose by a physician; he was also spiked playing baseball.

In both groups of children home discipline in general was characterized by inconsistency with explosive crack-downs. Neither group of parents as a whole could be called grossly punitive or cruel. Most of them impressed the staff as being basically warm people even when "bopping" their children. The general impression, however, was that the nonaccident parents were closer to the children and supervised them more closely. They had less trouble setting limits on their children's activities than did the accident parents. The accident parents seemed less in tune with their children and more distant; there did not seem, however, reason to refer to them as grossly "rejecting" parents. The homes of the accident children if anything were more congenial and the families seemed to have more fun together than did the nonaccident families. The distinction between "closeness" and "distance" in the parent-child relationships would seem to be important although this is a rather difficult finding to describe. It is apparent in photographs of mother and child in the 2 groups. In the nonaccident cases there is a "togetherness," mother and child look as if they were aware of each other. In the accident cases there is an "apartness" as if mother and child were each standing for the camera alone without much awareness of each other. These characteristics of nearness and distance are apparent in contacts with the child and parent.

One of the outstanding differences between the 2 groups of children is the way in which the accident children form pleasant if superficial relationships with adults. They seem to like to be with grown-ups, are friendly with them and have rather winning ways. The adult finds the accident

children likeable. The nonaccident children do not show this characteristic. They stick closer to their parents. It would seem that the nonaccident child is able to get more security in his relationships with his parents and does not have to turn in a pseudosocial independence to other adults. The nonaccident boy from the accident family has built up close relationships with adults in his father's family and does not show this characteristic with other adults. The nonaccident children are more dependent on their families, timid on the whole and not venturesome. The nonaccident children are submissive to authority; the accident children tend to accept authority with overt criticism at times, and particularly in the younger children there is a fluctuation between acceptance of adult authority and overt defiance.

As yet we have not discovered in our case material evidence that one group or the other is more fearful or has more pent-up aggression and resentment. Our material does not seem to justify any conclusion that the accident children have more guilt or self-destructive drives than the nonaccident. We have no evidence as yet to support the presence of primary conflict in the authority-hostility area. Perhaps further working over of our material, particularly the Thematic Apperception Test responses, may give some clues in these directions.

In going over the accumulated observations on the accident children it seemed as if they could be tentatively divided into 3 groups on the basis of their general behavior and reactions. These will be briefly summarized.

The accident child in one group is overactive and restless. He tends to be impulsive. He is well liked by adults but not well liked by his fellows. He does not get his dependency and security satisfactions at home. He tends to want to be older than his age and to overextend himself in his activities as he tries to keep up with his ambitions or seek acceptance by the group. He does not retreat from dangerous situations. He has a poor reaction to stress, becoming more impulsive and disorganized. Some of the accidents occur during this stress disorganization. Under stress he does not recognize or heed danger signals. As yet there has not seemed to be a specific type of situation which produces the disorganizing anxiety. The Rorschach data (many undifferentiated color responses) are in keeping with the breakdown of controls under strong emotional stress.

In order to see if there was any measurable breakdown of kinetic control under stress we have tried photographing the eye movements with an ophthalmograph during reading and again after threat of an electric shock to create a crude stress situation. Incomplete studies suggest that the accident children show gross changes in the eye movement patterns after the threat while the nonaccident children show lesser changes. It is planned to follow this with further study.

The accident repeater child described above would seem to get into situations where accidents were inevitable if he is under stress. The accidents then might well be unmotivated and the defect be a developmental one in the ego control mechanisms.

In our accident patients we could see 2 other types of children, one related to immaturity, lack of parental supervision, an insistence on the part of the child on autonomy and self-determination, and competition in activities with older children in a hazardous environment. The other is typified by a resentful, hostile boy who views his home as bleak and empty, a boy who prior to his beginning to have accidents 3 years ago presented a moderately severe conduct disorder. As this has cleared, his general overt behavior has become less resentful and rebellious. This boy does show pent-up rage and aggression; he does salvage some attention from his mother when he is injured. These accidents may well be motivated. In a longer series of cases it is possible that even more personality types would emerge.

The nonaccident group was more timid, submissive and controlled than most children. This may have been a fault of selection. It would seem better to obtain nonaccident children selected by a teacher and school nurse rather than rely on children already registered in the hospital clinic. Further studies should be done on a group of accident repeater children who are not on the extreme end of the accident scale. With such a group a larger number of children could be more easily obtained and the number of personality types might well be greater.

One difficulty experienced was our inability to get from the children or their parents much of the emotional overtones and feelings centered around the times of specific accidents. This may be related to the fact that many of the accidents were "cold" in that they had occurred some time before, but we were unable to get much information even when the accidents occurred during the course of the study. This might be related to the emotional and behavioral disorganization in the children at the time of the accidents, or even to the age of our subjects. It would seem well, however, to plan a study which would see children at the time they were brought in to the Emergency

Clinic. This kind of investigation might produce this information which we were unable to get consistently.

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Discussion

Miss Helen Ross, Chicago: "Accident proneness" was first suggested as a symptom several years ago, and soon became a popular diagnosis. The study made by Dr. Langford and his colleagues is among the first efforts to describe and explain accident proneness among children, and is therefore a highly laudable endeavor. We need evidence, scientifically established, of the existence of this symptom, and we need a study of its etiology. This study has attempted both. As in many similar efforts, it was not so easy to set up a goodly number of cases and, as Dr. Langford suggests, the conclusions reached in this progress report are not to be given undue weight. This study has further value in that an equal number of nonaccident children were studied also.

Since this study was done through a hospital, only those accidents bad enough for hospital care came to attention, yet children do have accidents that do not call for hospital service. It would be exceedingly interesting to know of Dr. Langford's group, how frequently the accident children in comparison with the nonaccident group had minor accidents at home and at school and of what nature. To establish with more precision who are the accident-prone children would require an extensive knowledge of the less serious hurts encountered in everyday life, not that these little accidents are in themselves important, but that they provide information about the general personality structure of the child. For if we find accident proneness is an entity, then we should learn how to recognize it earlier and following that, attempt to formulate an etiology which would help in the whole study of prevention.

A study of accident proneness in children may be approached in several ways. One is through observational studies. Parents, teachers, camp directors are in a better position to make such observations than the physician, because of their closer touch with the child. The summer camp offers an excellent opportunity for such observation. Years ago, before I knew the term "accident proneness," I recognized in my summer camp the tendency among certain children to have more than their share of accidents. "There goes Jane again," or "Who do you suppose fell out of the boat? Mary, of course." I had only girls in this camp.

I learned, too, that there were 2 ways to approach safety in the camp. One, to clear up hazards in the environment; 2, to consider what went on inside the many-accident child. More and more we learned how to handle the hazards, we turned to a consideration of the individual child. And so I came to isolate 3 general types who were prone to accidents: the show-off; the discouraged; the reckless. The show-off takes risks to prove himself not timid. In his insecurity, his judgment is poor; he overcompensates his timidity and fear. The discouraged child might react in 2 ways: he would retire from all competition and thus be safe, or he would enter an activity with the conviction he would fail, and fail he usually did. He is the blunderbuss child. The reckless child's attitude is often one of defiiance to rules of all kinds; he has a strong resistance to authority and plunges into activity defiantly and impulsively, often coming to grief.

Dr. Langford's categories are similar to the above. He has also given us some interesting hints as to the role of parental attitudes as causative factors. My own experience both clinically and as a matter of observation would corroborate his findings.

One factor we could observe at camp, which Dr. Langford had no opportunity to observe, was the "accident epidemic." Maybe girls are especially prone to this type of hysterical accident which often broke out during a camp season. A rash of sprained ankles was always anticipated after a favorite councillor or a popular older girl would suffer some mishap to her ankle, particularly if done in a dramatic way. This is mentioned here in order to give some weight to the mechanism of identification in accidents, which was noted by Dr. Langford in his paper.

The second approach to this kind of study is that used by Dr. Langford, a descriptive statistical study on a broad basis which yields information about the symptom, some guides for further studies, and some suggestions for preventive measures.

The third approach to our subject is the purely psychodynamic, suggested also by Dr. Langford's findings. By means of more intensive studies of a few cases, we might learn much more about the etiology of this symptom in all its ramifications. We would thus see the interaction of parental attitudes with children's behavior, the influence of specific trauma, the influence of identification with the parent or siblings, the use of accident to gain love and attention, the selection of this masochistic solution to meet emotional needs, and so on.

Every study of accident proneness in children should arouse us, as this one does, to the preventive aspects of the subject.

Dr. Reynold A. Jensen, Minneapolis: Those of us here tonight are fully aware of the real importance of the general problem of accidents and injuries to children in our country today—one about which everyone should be concerned. In reality it is one of our major current medical problems. For example in the State of Minnesota, accidents accounted for over 33% of all deaths in children from 1 to 14 years of age in 1950.

While the over-all problem of accident and injury in children is important, that of the child who is injury-prone is of especial significance since so little is known about it. It is to this particular group Dr. Langford and his associates have directed their attention and effort. The report is a pilot study, which all of us should not only welcome now but also for future reference.

As human nature and behavior is exceedingly complex, it is difficult to study it scientifically due to the large number of variables involved. Many of these have been anticipated and included in this study. The approach has been on a broad base including not only historical data on the child, parents and family, but also careful, detailed physical, neurologic, as well as psychologic studies and personal interviews; also a contrast or comparison group has been included—a must in scientific research.

It has occurred to me more definitive data regarding parental attitudes, personalities and family organization might have been collected by the use of the several rating scales available and the projective tests such as the Rorschach and Minnesota Multiphasic. These might prove useful. While Dr. Langford and his group report few positive physical findings, it occurred to me the judicious use of metrazol® might have brought out latent differences in the electroencephalographic findings.

Dr. Langford has wisely avoided formulating conclusions on the basis of the work done to date. There are several contributions this study has made to date:

1. Much work has been done in defining the injury-prone child. The task was a difficult one. The careful thought given this, as well as the many other intrinsic factors, may well serve as an important guide to subsequent studies made by others.

2. Further evidence the injury-prone child is different from his peers has been presented. What this difference is remains to be answered.

3. The need for sharpening current instruments of study is obvious. It may be necessary to develop others. The use of the ophthalmograph suggests possibilities for many clearly delineating definitive important physical differences between the injury-prone child and his peers. While these may appear minimal, they may prove significant.

4. Several pitfalls have been clearly delineated which should be avoided by all interested in research involving children. Among the most obvious are (a) the fallacy of reasoning backward to children from studies done on adults with comparable problems, (b) the need for exercising caution in formulating conclusions or interpretations too early and (c) the danger of making "too much of too little."

5. A standard has been set for future studies.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous."

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

Dr. Walter B. Martin is a practicing physician in Norfolk, Va., and trustee of the American Medical Association. His letter is an expansion of remarks made at a meeting of Medical Consultants to one of the Armed Services about the competition for house staff between civilian hospitals and military, veterans' and public health service hospitals.

DEAR DR. HARPER:

Since you were interested in some casual remarks I made concerning the dispersion of our medical training resources in this country, I am going to impose on your patience by further expanding the subject.

Much has been said and written lately about the shortage of physicians and allied technical personnel. In spite of the fact that we have more physicians per thousand population than any other major country, we are constantly being told that we face a critical shortage of doctors and that something must be done about it. It is true that the demand of the general population for health services has vastly increased. Whether this increase is due to an intelligent understanding by more people of what good medicine can offer, or to overindulgence in the luxuries of medicine, may be open to question. The fact remains, however, that in spite of a constant increasing number of doctors per thousand, and greater productivity of the individual physician by reason of better transportation, improved mechanical aids, and an increased number of technical assistants, the load on medicine steadily increased. This load has been diminished in no way by dividing "Gaul" not into three parts, but into six.

This alleged shortage of doctors and other health personnel is partly due to faulty distribution but it is also to a considerable extent an artificial creation brought about by unnecessary expansion of government medical services. Most of the proposals for correc-

tion of the situation have not sufficiently emphasized this fact, but have been content to urge the spending of more federal money for the purpose of building and financing more medical schools, subsidizing existing ones, and training more personnel in related fields. Let us take a look at the major medical activities of our central government.

This country has developed a large voluntary hospital medical training program that centers around the medical schools and voluntary teaching hospitals. This system is partly supported by the Federal government through the Hill-Burton Act, and by various grants to medical schools for research. In addition to this however the Federal government maintains five major medical training activities, for intern and residents, under the Army, Navy, Air Force, Veterans Bureau, and the Public Health Service. These medical services were designed originally to meet the need of certain groups that, due to their particular functions or duties, could not come under a civilian program. The activities of these special medical services, however, have been vastly expanded by drawing in to their sphere a constantly increasing number of civilians who previously had been cared for by civilian medicine. Where formerly they relied on the civilian training program to provide their highly skilled specialist, each of these government services has now embarked on a training program of its own. In order to qualify for resident and intern training, it is necessary for service hospitals to have diversified clinical material. Good medical training cannot be based only on diseases afflicting young men of military age or veterans with chronic diseases. Consequently there has been an increasing pressure to draw into these hospitals the dependents of service personnel, dependents of the coast guard, and non-service connected general, medical and surgical cases among the veterans.

In the case of the Armed Forces the medical care program for dependents of service personel is based on a very slender foundation of law. In 1884 Congress authorized army physicians to give medical care to dependents of military personnel in isolated posts where other facilities were not available and if army beds were available. By a series of interpretations and amendments, this law has been extended to the Navy, the Air Corps, and the Public Health Service. It has been further extended to cover the employees of private contractors on construction projects over seas. Throughout the United States, service hospitals located near large urban area that are well supplied with civilian hospitals, are still drawing into their folds a constantly growing number of civilian patients. At this time I am not considering the question of whether or not the Federal government is properly responsible for the medical care of all dependents of military personnel, but am merely pointing out the effect of the present procedure.

Under the law governing the hospitalization of veterans, the veteran hospitals are allowed to care for non-service connected cases, if the veteran is unable to pay for his own care, and if beds are available. Through this loophole have crept thousands of non-service connected cases, in all stages of economic affluence until now over 87% of all general, medical and surgical admissions into veteran hospitals are non-service connected. When one considers that 34.4% of all veteran hospital beds are occupied by general, medical and surgical cases, and that they remain for an average of 30.8 days, it would seem that the taxpayer is contributing a sizable sum for the maintenance of a training program in the veterans hospitals. Each service will defend to the utmost its need for a complete medical training program, in order to supply their particular service with the necessary number of trained men. If such programs are to be acceptable they must have access to a diversified group of patients of both sex, and of all ages in the general, medical and surgical categories. To procure this diversification they must continue

to drive for an increased number of dependents of service personnel and more and more non-service connected veterans' cases.

To support all of this, more doctors are needed in all of the branches of medicine, more nurses, and more technicians in various categories. To take care of the situation there must be more hospitals and dispensaries, more equipment, and more facilities of all kinds. To obtain the needed technical personnel, these various government hospitals compete not only with each other, but with all of the civilian hospitals and institutions. To secure the doctors necessary for their purpose, the Armed Forces must strive for a very considerable additional quota of physicians now obtainable under the draft law. The blocking effect of recruitment difficulties no longer exists nor does the element of cost play much of a part. Patriotic motives and humane considerations compel us to support a law that permits the orderly withdrawal from civil life of the number of physicians necessary to provide the best medical care possible for those in uniform even though this results in further expanding medical service to civilians in government facilities.

But this is not all. The government hospitals are in competition with civilian hospitals, not only for personnel, but also for patients. Here we have a remarkable situation. The Federal government, aided by states and localities, is spending millions of dollars under the Hill-Burton Act, in civilian hospital construction. At the same time the Federal government is making it difficult for these civilian hospitals to operate at a reasonable cost, since many patients that would normally flow into civilian hospitals are diverted from these community enterprises into hospitals wholly supported by the Federal government. This does not make sense to the taxpayer, or to anyone, from the standpoint of producing good medical care for the American people as a whole. It has resulted in a wasteful duplication of hospital facilities, unwarranted dispersion of needed personnel and an increased cost of hospital and medical care for those who pay their way. The integrity of our great voluntary teaching program is threatened. The present policy is producing a centripetal force that is drawing more and more patients and more and more physicians and other health personnel into the Federal vortex.

I have no happy and immediate solution of the problems presented. I am quite sure, however, that the situation is not a static one but will steadily become more aggravated unless there is a complete reversal of the present trend. Such a change will naturally not receive the support of the principal agencies involved but can only be brought about by a united effort of the whole body of medicine, supported by taxpaying citizens.

WALTER B. MARTIN, M.D.
Norfolk, Va.

TRENDS

By John P. Hubbard, M.D., *Contributing Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

A YEAR OF PROGRESS IN PEDIATRIC RESEARCH SUPPORTED BY PLAYTEX PARK RESEARCH INSTITUTE*

THE origins and initial operations of Playtex Park Research Institute in support of pediatric research were reported in this column a year and a half ago.[1] When the Institute was founded by the International Latex Corporation it was described as "an experiment in industrial giving." The accomplishments of the Institute to date justify the faith that the sponsor and the governing board had in the concept that industry and medicine can work as a team for the common good with great effectiveness.

The medical world is well aware of the ever present necessity for the private augmentation of the pitifully small existing funds for pediatric research. It is indeed fortunate that Playtex Park Research Institute is the beneficiary of its sponsor's realistic and farsighted approach to this need. In the short period of less than three years, the Institute has received almost $700,000.00 in commitments from the International Latex Corporation which is indeed a generous contribution to the advancement of pediatric knowledge. This has made the Institute's sponsor the largest private source of funds for pediatric research in the country, and possibly the world. The sponsor insists on taking no part in deciding how this money is spent. Reflecting these wishes, such jurisdiction is placed solely in the hands of the 25 physicians comprising the Institute's Board of Governors.

The constructive good that accrues from such support is best reflected in the fact that more than one-third of the grantees who have received Institute support for a year or longer have had papers on their investigations published in various outstanding medical journals of the world, one of them by invitation in a leading European journal.

Even more impressive are the 34 papers by grantees which have been presented by them before 29 scientific groups or organizations and which reported on investigations supported by Institute grants. There also are 16 papers or books by grantees which have been scheduled for publication or are in the process of preparation.

The work of the Institute's grantees has received even more signal recognition. One of its grants made possible the preparation of the basic material for an exhibit on the pathology of perinatal death, presented at the American Congress on Obstetrics and Gynecology last spring. This exhibit was awarded third prize.

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* This article was prepared by the Playtex Park Research Institute and approved by its Executive Committee:

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Charles F. McKhann, M.D., Vice Chairman
Joseph Stokes, Jr., M.D.
W. O. Heinze, Treasurer
Lawrence C. Salter, Secretary

[1] Pediatrics 8:738-740 (Nov.) 1951.

Space does not permit a detailed description of the medical advances during the past year to which Institute grantees have contributed. One, perhaps, merits particular mention.

On October 16, 1951, medical history was made when, for the first time, surgeons saw and were able to study the mitral valve functioning in situ. An Institute grant to Dr. Elliott S. Hurwitt at Montefiore Hospital, New York, had helped finance the production of a motion picture, in color, entitled "A Cinematographic Study of the Function of the Mitral Valve in Situ." The project was carried out by Dr. Hurwitt, Dr. Adrian Kantrowitz, who developed the artificial heart used in taking the film, and Mr. Antol Herskovitz, the hospital photographer. The film was first shown on October 16 at the hospital as part of the New York Academy of Medicine Postgraduate Fortnightly on Cardiovascular Diseases, and subsequently before a large number of other scientific groups and medical schools. Later it was revised for teaching purposes in cooperation with the Medical Audio-Visual Institute of the Association of American Medical Colleges and now is being distributed by the latter. In the film credit is given Playtex Park Research Institute for support of this project.

As the Medical Audio-Visual Institute reports in a recent bulletin, "This research film, modified for teaching purposes, shows in slow motion, movements of the mitral valve filmed through atrial and ventricular openings in a dog heart rendered bloodless in the left chambers by means of a newly developed circulatory shunt technique. Simple in design and conclusions, the film is well oriented by means of simple animation and postmortem heart demonstration, for effective use with students of cardiac physiology, and its over-all filmcraft is of a high order." The film is particularly recommended for students in medical schools, allied professional schools, colleges, internists, surgical residents, and cardiac surgeons.

A listing of the titles of the grantees' papers which already have appeared in medical literature will give some idea of the scope of the advances in pediatric knowledge in which these grantees are playing a role. References to these papers are shown below.

Of equal importance in an evaluation of the contributions of the Institute to pediatrics are the number of individuals who have been able to continue in this research field due to financial aid received from the Institute. In many instances limited institutional budgets have not made it possible to pay a living income to investigators of promise in the field of pediatrics. Grants from the Institute have sufficiently augmented the salaries of several investigators so that they have been able to remain in the field of their basic interest rather than having had to enter into other endeavors. This far-sighted Institute policy is paying off. It is reflected not only in the scientific contributions being made by grantees but also in the academic promotions that already have been forthcoming to several of them.

In the previous report, this column told of the grants by the Institute which then had been made. Most of them are still in effect. The following additional grants subsequently have been authorized by the Institute's Board of Governors:

Studies of the Pathogenesis of Erythroblastosis Foetalis and Kernicterus, St. Louis University School of Medicine.

Cerebral Blood Flow and Metabolism in Infancy and Children, Children's Hospital of Philadelphia.

Studies of Mice and Rabbits with Neuromuscular Abnormalities, Roscoe B. Jackson Memorial Laboratory.

Metabolic Effects of Polypeptid Derivatives of Various Hormones, University of California School of Medicine.

Pediatric Hematology, The Children's Hospital of Michigan.

Causes and Prevention of Stillbirth and Neonatal Death, Johns Hopkins University School of Medicine.

Studies on the Normal and Pathological Physiology of the Plasma Proteins, Children's Medical Center, Boston.

Investigation of Cerebral Metabolism, Research Foundation of Children's Hospital of Washington, D.C.

Studies of Viral Infections of the Neonatal Period with Particular Reference to the Prevalence of Coxsackie Virus Infection, The Children's Hospital of Buffalo.

Studies in Chemical Growth, Southwestern Medical School of the University of Texas.

Investigation into Body Mechanism Regulating Cell Composition, Yale University School of Medicine.

Medical Therapeutic Engineering in the Field of Pediatrics, University of Buffalo School of Medicine, Chronic Disease Institute.

Studies of Pathological Physiology of Liver Disease in Children, Beth Israel Hospital, Boston.

Continuation of Studies of Animals and Humans for Producing a Complete Bypass of the Heart and Lungs so that Intra-Cardiac Surgery May be Performed Under Direct Vision, University of Cincinnati College of Medicine.

Chemotherapy of Cancer in Children, Hospital Infantil, Mexico City.

It should be emphasized that, for obvious reasons, the above listed grants are by title rather than the name of the grantee. From the point of view of the Board of Governors the field of investigation is of secondary importance; their primary concern is in pediatric research talent.

Recently the Board of Governors of Playtex Park Research Institute further defined its grant-making policy by inaugurating a new and significant procedure. Each member of the Board has been specifically requested to seek out in his or her own locality potential grantees with challenging new ideas in the field of pediatrics.

To implement this policy, seven new members have been elected to the Board, including one from Canada and one from Mexico. Thus all of North America has been brought into the scope of the Institute's activities. Dr. Sidney Farber, Professor of Pathology at Children's Hospital, Harvard Medical School, and the Institute's Board chairman, in announcing the increased membership and the new program, said:

"Since the most rapid progress in the solution of the problems still regarded as 'incurable' will come from new research with the aid of new techniques, it is imperative that the Institute's Board learn of able research talent, wherever located, as soon as possible. With the newly elected members, the Board now has the widespread geographical representation required to carry out effectively the Institute's policy of finding and selecting grantees on the basis of ability rather than making grants solely for work in a specific field of investigation. The aim of this Foundation is to support men with ideas—not specific projects to which a research worker is attached."

Mr. W. O. Heinze, the Institute's treasurer and president of its sponsoring company, in endorsing the new program said:

"The need for finding gifted young doctors with the exploratory type of mind that is essential to basic research is most urgent. It is hoped that men of real promise will be

encouraged to apply for grants. Science needs such men, and such ability must be found and supported if we are to help solve the many remaining mysteries of childhood diseases."

In the constant unraveling of the many baffling problems of child health, it is gratifying to note the increasingly important part that the Playtex Park Research Institute is playing in the progress in pediatric research.

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NEWS AND ANNOUNCEMENTS

A course in pediatrics will be conducted at St. Christopher's Hospital for Children, Philadelphia, by the Pediatric Department of Temple University School of Medicine on June 10 to 13. Each half-day session will be devoted to a single phase of pediatric medicine. For information regarding enrollment, registration fee, etc., write to St. Christopher's Hospital for Children, 2600 N. Lawrence St., Philadelphia.

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Memorial Center for Cancer and Allied Diseases, Pediatric Department, announces a comprehensive 3 day course April 29, 30 and May 1, 1953 for pediatricians, general practitioners, health officers. Current developments and established methods in diagnosis, differential diagnosis and management of benign and malignant tumors, Hodgkin's disease, leukemia and reticuloendothelioses in childhood are included.

Content of course: Demonstrations, examinations of children in pediatric, surgical, chemotherapy, radiotherapy clinics; ward rounds and seminars under the direction of the staffs of Memorial Hospital and Sloan-Kettering Institute for Cancer Research. Fee $35.00. For information address: Director, Pediatric Service, Memorial Center, 444 E. 68th St., New York City.

BOOK REVIEW

SURVEY OF CLINICAL PEDIATRICS, Lawrence B. Slobody, M.D., New York, McGraw-Hill Book Company, 1952, $7.50, 471 pp.

According to the author's preface, this book grew out of notes prepared for the teaching of pediatrics by the author and his colleagues at the various New York institutions with which they are associated, and is designed to help the student and the practitioner focus upon the highlights and relationships of pediatrics. Its 23 separate sections would seem to cover quite satisfactorily the great majority of the pediatiric problems the physician meets in his office and hospital practice.

The material is presented in a rather unique fashion for a textbook. Much of it is in outline form, but all of it is stripped down to the central core of information or fact about the topic under discussion. Thus, the significant features of a specific disease are listed as a series of subheadings. Laboratory aids and suggested treatment are similarly listed. Differential diagnosis and special bits of information are included wherever indicated.

The book contains no illustrations, but has 22 useful tables. At the end of each section are questions and true-and-false statements which are probably more useful to the student facing an examination than to the physician in practice.

In the opinion of the reviewer, the information given is accurate and up-to-date, and the distribution of emphasis on the various subjects presented is excellent. Medical students, interns and residents in pediatric hospitals, and general practitioners who want a source of quick reference to pediatric information should find this a useful book.